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PNEUMATOSIS CYSTOIDES INTESTINALIS IN INFANCY

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PNEUMATOSIS cystoides intestinalis (pneumatosis cystoides intestini, pneumatosis cystoides intestinorum, intestinal emphysema, abdominal gas cysts, intestinal gas cysts) is a distinctive morphologic entity of obscure origin and rare occurrence which is characterized by the presence of gas cysts within the bowel wall and sometimes within the adjacent mesenteric fat and regional lymph nodes. Clinically, it possesses no specific or diagnostic symptomatology and has a bizarre age distribution in that it occurs predominantly in infants and middle-aged people. In the latter, however, the lesions are predominantly serosal in distribution whereas in the former they occur predominantly within the mucosa and submucosa. It is generally accepted that the gas cysts represent lymphatic channels distended with gas. In infants this process is associated either with no inflammatory reaction in the cyst walls or, if there is some, it is minimal in amount and neutrophilic in character. In adults, on the other hand, there is always an associated inflammatory reaction which is essentially chronic in nature and often of foreign body type. Curiously enough, in infants pneumatosis is invariably associated with acute enteritis, whereas in adults, although occasionally primary, it is most frequently associated with stenosing peptic ulcer, either gastric or duodenal, and less frequently with carcinoma of the stomach, intestinal tuberculosis, acute and chronic appendicitis and enteritis and fibrous adhesive bands.

A perusal of the literature reveals that pneumatosis is observed much more frequently in adults than in infants, at an approximate ratio of 7 to 1. Koss,[1] who made an extensive survey of the literature, collected 255 cases, thirty-one of which were in infants. Of the latter, Koss accepted only six cases as being genuine, preferring to regard the remainder as probably terminal events, influenced undoubtedly by the apparent dissimilarities, already enumerated above, between the infantile and adult variants.

Although from a clinical and economic standpoint pneumatosis cystoides intestinalis is certainly an unimportant condition, from a purely scientific view it represents another mechanism of disease, certainly peculiar to the intestine, which challenges intellect and demands understanding. Moreover, an understanding of the

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apparently unimportant often leads to an understanding of larger and more important matters, and in this case possibly even to a greater understanding of both the normal and pathologic physiology of the bowel. It is with this in mind that the following unique case of pneumatosis cystoides intestinalis associated with congenital megacolon in an infant is presented.

CASE REPORT

This 5-month-old white male infant was born in France on Sept. 16, 1952. Pregnancy and labor were normal and uneventful. The birth weight was 7 pounds 8 ounces. However, soon after taking the infant home, the mother observed that the baby had some stool in each diaper change. The stool was of a pasty consistency, gray to brown in color, and exceptionally malodorous, but apparently not fatty. At 2 months of age the infant did not have a bowel movement for five days in spite of enemas. He was taken to a dispensary, where impactions were broken up. This was the beginning of a cycle consisting of an eight- to nine-day period of constipation despite enemas, followed by hard stools, soft semisolid stools in great abundance, and then another eight to nine days of constipation, etc. He was admitted to the Fifth General Hospital on Jan. 9, 1953, where he was thought to have congenital megacolon. Subsequently when 5 months old he was transferred to Brooke Army Hospital where he was admitted on Feb. 24, 1953.

Physical examination disclosed a malnourished infant who weighed 10 pounds 7 ounces and measured 25 inches in length. The temperature was 99° F. and the heart rate 120. The abdomen was protuberant and the rectum was filled with hard feces. The remainder of the physical examination was essentially noncontributory.

Daily enemas were required for stool elimination. Barium enemas performed on Feb. 24, March 5, and March 12, 1953, were reported as indicating the presence of congenital megacolon with malrotation of the colon. A flat plate of the abdomen taken on March 29, 1953, revealed a radiolucent line which followed the wall of the small intestine. This was interpreted by Captain Elwyn Cavin as possibly representing pneumatosis

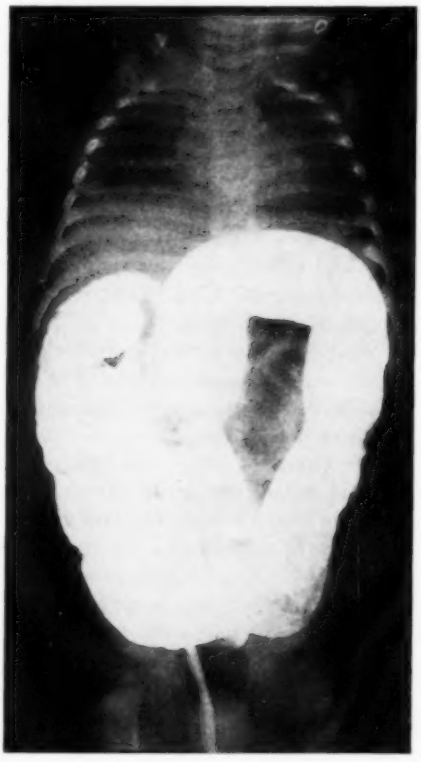
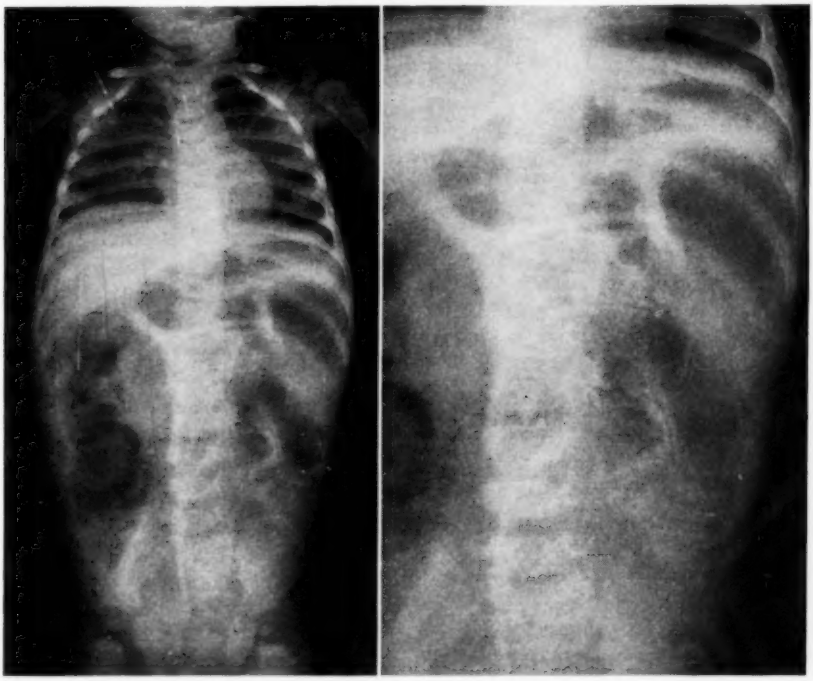


Fig. 1.—Barium enema showing congenital megacolon associated with malrotation of the colon. The sigmoid colon occupies the right side of the abdomen and the narrowed segment beneath the liver was produced by extrinsic fibrous bands which were lysed at laparotomy.

cystoides intestinalis. An exploratory laparotomy was performed on April 1, 1953, when pneumatosis cystoides intestinalis of much of the wall of

the small and large bowel was revealed. In addition, considerable distention of both the large and small bowel was noted. There was incomplete rotation of the large bowel, with the cecum under the liver. The sigmoid occupied the right lateral gutter. The large bowel was freed from several adhesive bands which were present, and placed in its normal position but not tacked down. Postoperatively, the child had no bowel movements and moderate distention persisted. On April 6, 1953, the child was marasmic and passed tomato-juice-like stools which were benzidine-positive. The child died the same day.



A. *B.*

Fig. 2.—*A* and *B*, Flat plate of abdomen showing dilated loops of small bowel whose walls are delineated by a double contour line.

Necropsy Findings.—The body was that of a malnourished, dehydrated, poorly developed, white male infant, said to be 5 months of age, weighing 4,000 grams and measuring 41 cm. from crown to rump and 65 cm. from crown to heel, in whom rigor mortis was absent. The skull was symmetrical and the anterior fontanel was considerably depressed. The face was wizened and the eyes were sunken. The abdomen was considerably distended, with some eversion of the umbilicus, and presented a recent upper abdominal, left pararectus surgical incision. Upon making the usual "Y"-shaped incision, complete absence of panniculus adiposus was noted and the subcutaneous tissue and underlying musculature were exceedingly pale and dry.

Peritoneal Cavity: The peritoneal cavity contained 50 c.c. of turbid, blood-tinged, yellow fluid. The entire

gastrointestinal tract was greatly dilated, the sigmoid colon most markedly so, appearing as a redundant, horseshoe-shaped loop of bowel within the abdominal cavity proper, looping first to the right and then to the left to continue on as the descending colon in the left iliae fossa. The descending colon occupied its usual site and possessed its usual relationships, but the transverse and ascending colon possessed a large mesentery and lay free in the left side of the abdominal cavity. The colonic mesentery presented within its root a large ovoid hiatus which measured 3 cm. in diameter and possessed smooth, rolled edges. The small intestine occupied the central portion as well as the entire right half of the abdominal cavity. The small intestine, from the ligament of Treitz to within 30 cm. of the ileocecal valve, presented numerous subserosal gas cysts ranging up to 1.5 cm. in diameter, which extended into the root of the mesentery and gave the bowel a spongy appearance and consistency. The peritoneum over the small and large bowel was lusterless, for the most part.

The thymus, heart, liver, spleen, and kidneys, as well as the pancreas, right adrenal gland, thyroid, pituitary, and brain showed no remarkable gross pathologic alteration. The lungs exhibited focal areas of atelectasis within the apical portion of the right upper lobe and the posterior portions of both lower lobes. The left adrenal gland was hemorrhagic in appearance. On section the hemorrhage was noted to be predominantly medullary in location.

Gastrointestinal Tract: The esophagus exhibited no significant gross pathologic changes. The stomach was tremendously dilated and its lumen was filled with abundant amounts of curds admixed with pale green bile. There was complete loss of rugal pattern and the wall was considerably thinned, measuring 0.1 cm. in thickness. No mucosal ulcerations or gas cysts were noted. The duodenum was slightly dilated and presented no other significant changes. The entire small bowel was considerably dilated and measured 4.5 cm. in circumference. From the ligament of Treitz to within 30 cm. of the ileocecal valve, the small intestine presented numerous subserosal gas cysts ranging up to 1.5 cm. in diameter, which extended into the root of the mesentery and gave the bowel a sponge-rubber-like appearance and consistency.

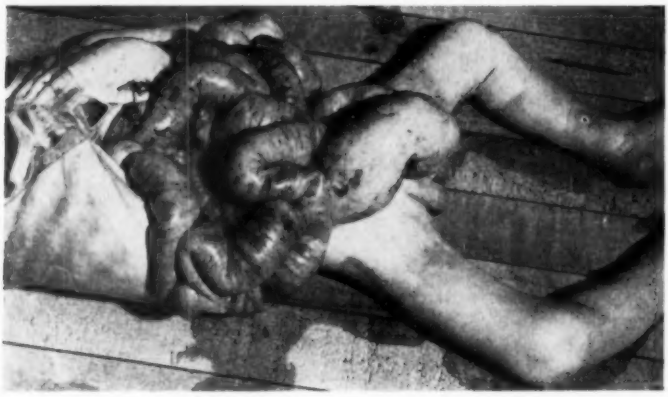


Fig. 3.—Body at autopsy, showing congenital sigmoidal megacolon as well as considerable dilatation of the small bowel. The gas cysts within the latter are not obvious in this picture.

These gas cysts deflated rapidly with a "poof" when pricked, indicating the presence of a positive pressure within them. On opening the small bowel, its lumen was seen to be filled with liquid green stool which was foamy in character. When this was cleared out, numerous submucosal, translucent gas cysts were noted, ranging from pinhead-size to 0.4 cm. in diameter, which distorted the villus folds and gave an undulating appearance and cushiony consistency to the mucosa. The latter was pale pink in color and injected in parts, with no gross evidence of any epithelial ulceration. The bowel wall measured up to 0.4 cm. in thickness and the gas cysts appeared to be predominantly submucosal in distribution. The distal 30 cm. of ileum was completely free of gas cysts and presented the normal ileal architecture. The colon was also completely free of gas cysts, but was unevenly dilated throughout, the cecum and ascending colon measuring 5.5 cm. in circumference, the transverse colon measuring 8 cm. and the descending colon measuring 4 cm. in circumference. The greatest dilatation, however, was exhibited by the sigmoid, which was redundant, moderately thick-walled, and measured 10.5 cm. in circumference. The rectum measured 4 cm. in circumference. On opening the colon, its lumen was patent throughout and it was seen to contain a small amount of pasty, blood-tinged, grayish brown stool. The rectum and anus were similarly patent, with no evidence of any organic obstruction. However, at the rectosigmoid junction there was a concentric ring of muscular hypertrophy which caused slight luminal constriction at this point. The mucosa was intact throughout, without any gross evidence of epithelial ulceration. The haustral pattern within the ascending, transverse, and descending colon was still identifiable, but completely absent within the sigmoidal portion. Here, the haustral pattern was completely obliterated and the wall somewhat thickened.

Mesenteric Lymph Nodes: The mesenteric lymph nodes were moderately enlarged, ranging up to 1 cm. in diameter. They were discrete, and soft in consistency. On section, their cut surfaces were moist, succulent, and café au lait in color.

Special Laboratory Procedures: Aerobic and anaerobic cultures made from gas obtained from several of the gas cysts demonstrated the presence of *Esch. coli,* probably a contaminant.

Microscopic Examination.—Except for marked vascular congestion, sections of heart, thymus, liver, spleen, pancreas, kidneys, urinary bladder, right adrenal gland, thyroid and brain showed essentially no remarkable histopathologic changes. Sections taken from both lungs confirmed the presence of many scattered areas of focal atelectasis. A section of left adrenal gland revealed the medulla and major portion of the contiguous cortex to be disrupted by an extensive fresh hemorrhage which, in places, had broken through the entire thickness of the cortex to involve the periadrenal adipose tissue.

Gastrointestinal Tract: Sections of stomach displayed considerable mucosal and submucosal vascular congestion. Otherwise, there were essentially no noteworthy histopathologic changes present. All sections of small intestine, including that portion uninvolved by gas cysts, showed an intact mucosa with considerable edema of the villi, which contained dilated lymphatic channels as well as small to moderate numbers of neutrophils occasionally interspersed with eosinophils. There were no gas cysts within the mucosa. The muscularis mucosae was also intact, but it was often displaced upward by the presence of numerous, empty cystic cavities within the submucosa. These cystic spaces were of varying size and shape, sometimes quite huge, and were either partially or completely lined by a unilayered, flattened endothelium—undoubtedly representing cystically dilated lymph vessels. They were often in close prox-

imity to one another, being separated from each other by exceedingly thin fibrous connective tissue septa which were often hyalinized. In places these septa were disrupted, with resultant union of some of the cystic spaces. The latter, for the most part, were completely unassociated with any inflammatory reaction, although occasionally their walls were focally and diffusely infiltrated with small to moderate numbers of neutrophils. In addition, inter-

Fig. 4.

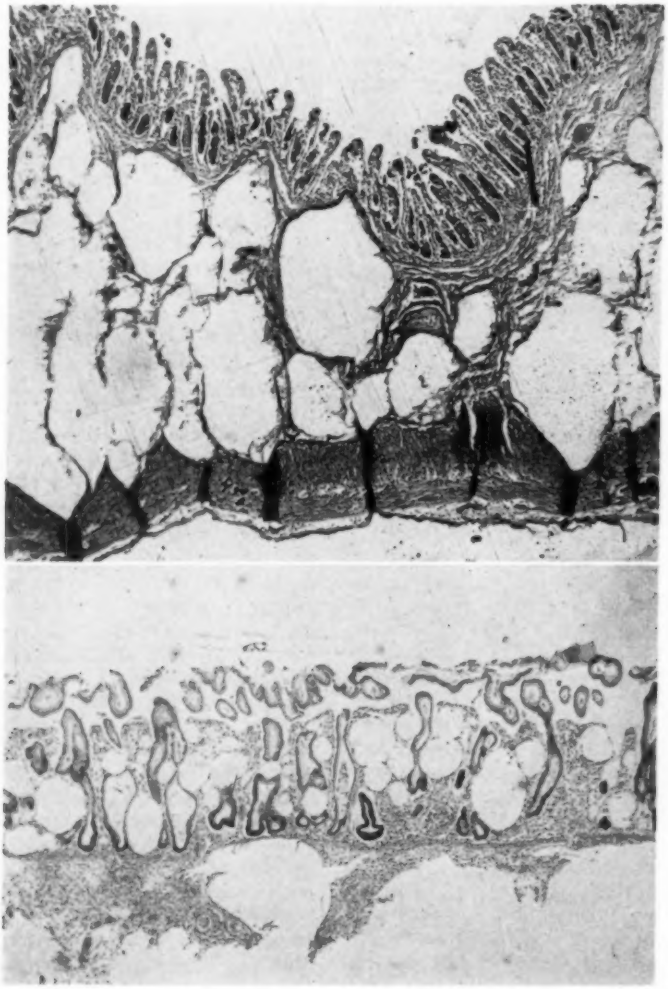


Fig. 5.

Fig. 4.—Section of small bowel showing gas cysts within the submucosa. Note the absence of gas cysts from the muscularis mucosae and muscularis. (×30; reduced 1/10.)

Fig. 5.—Section of small bowel from case autopsied by Captain P. T. Flynn, showing gas cysts within the mucosa and submucosa, in which the lymphatic nature of the lesion is readily apparent. (×30; reduced 1/10.)

spersed among these cystic cavities, occasional dilated lymphatic vessels were observed, some of which contained small clumps of neutrophils. The submucosal vessels throughout were markedly dilated and congested, with occasional small focal areas of fresh hemorrhage here and there between the cysts. The muscularis was markedly narrowed by the pressure of the cystic spaces within the submucosa. The narrowing was irregular and appeared to be most pronounced along the course of the blood vessels, along whose surrounding connective tissue the gas cysts extended. No gas cysts were noted within the muscularis. The subserosal connective tissue was edematous and showed mild to moderate fibroblastic proliferation with some intermingling of histiocytes and neutrophils. Here and there within the subserosal connective tissue occasional gas cysts were noted which were similar in appearance to those observed within the submucosa. The serosa itself was covered by a narrow layer of hyalinized fibrin. Gram's stains were negative for bacteria. Sections of sigmoid colon revealed an intact but apparently flattened lining epithelium. The muscularis mucosae as well as the muscularis was markedly hypertrophied, the internal circular layer of the latter showing the greatest degree of enlargement. The plexi of Auerbach and Meissner appeared to be present in adequate, if not reduced, numbers. The subserosal connective tissue was edematous and showed moderate fibroplastic proliferation. The serosa itself was covered in places by an exceedingly thin layer of hyalinized fibrin. Sections taken from the rectosigmoid junction showed the grossly described area of concentric muscular hypertrophy to be caused by marked thickening of the internal circular muscle. The plexi of Auerbach and Meissner in this region appeared to be present in unreduced numbers.

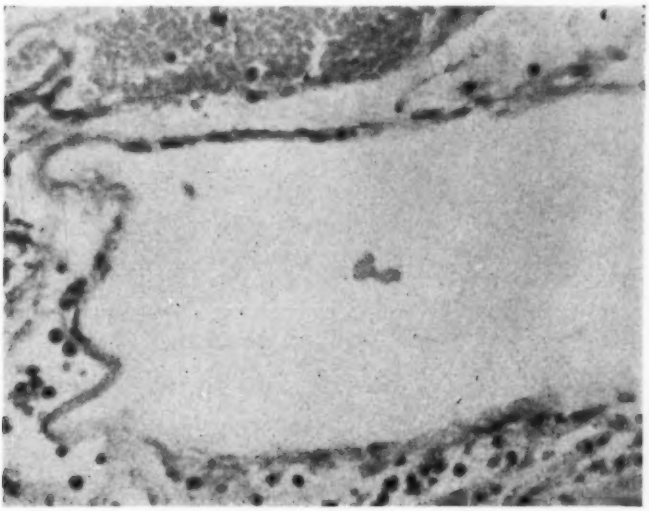
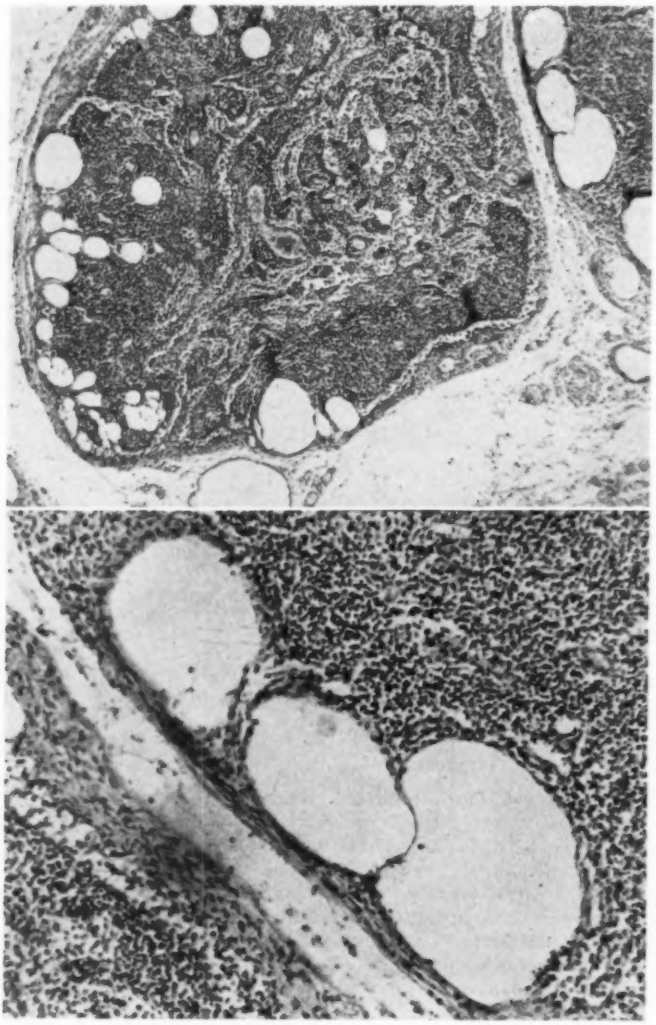


Fig. 6.—Portion of gas cyst showing its lining of flattened endothelial cells. (×300; reduced ⅛.)

Mesenteric Lymph Nodes: Sections revealed the normal lymph node architecture to be either completely or partially disrupted by the presence of numerous cystically dilated spaces lined by a unilayered flattened endo-

thelium. These appeared to represent hugely dilated lymph sinuses, with remnants of compressed lymphoid tissue and trabeculae between them which contained in places a diffuse scattering of neutrophils and large mononuclear cells. In addition, within the contiguous mesenteric adipose tissue several cystically dilated lymph channels were also noted. These were occasionally associated with the presence of small numbers of diffusely

A.



B.

Fig. 7.—*A*, Section of mesenteric lymph node showing minimal involvement by gas cysts. Note their predominance at the periphery of the node where the peripheral sinus is normally situated. (×30; reduced ⅛.) *B*, High-power magnification of *A*. (×105; reduced ⅛.)

scattered neutrophils and large mononuclear cells in the surrounding tissue. Gram's stains were negative for bacteria.

Anatomic Diagnoses.—Congenital megacolon (sigmoid), incomplete rotation of colon, acute catarrhal enteritis, acute mesenteric lymphadenitis, pneumatosis cystoides intestinalis, massive hemorrhage of left adrenal gland, malnutrition and dehydration, and bilateral focal pulmonary atelectasis.

DISCUSSION

Heretofore, several major theories with various modifications have been offered to explain the pathogenesis of the lesions of pneumatosis. These may be classified broadly as: (1) mechanical, (2) bacterial, and (3) chemical. The mechanical theory explains the development of the gas cysts on the basis of a mucosal break or ulcer and the entrance thereby of gas from the intestinal lumen into the tissues and lymphatics of the bowel wall. This theory presupposes the presence of increased intraluminal gas pressures, sufficient in any case to overcome tissue resistance. Recently, Stiennon[2] offered a modification of this concept in which he postulated that the gas penetrated the stomach wall through a mucosal ulceration to involve the subserosal connective tissue directly and then spread along the mesentery to involve segments of bowel remotely situated from the area of mucosal ulceration. The bacterial theory relies in part on the mechanical theory. Here, the bacteria cause mucosal ulcerations, gain entrance to the tissues and their lymphatics, and by their activity produce gas there. The chemical theory, on the other hand, presumes that the gas is produced as a result of defective carbohydrate metabolism which causes the liberation of carbon dioxide within the lymphatics.[3] Other variants of this approach to the subject, including Bang's[4] concept of neoplasia, generously endow the lining cells of the cysts with the ability to secrete gas, much after the fashion of air bladders in fish.

In evaluating any morphologic alteration in pathology, it must be readily apparent that the factors of realization may be one or more in number, acting either individually, concurrently, or successively. Furthermore, any morbid change in morphology may be produced by several entirely different and unrelated agents acting independently of each other but setting in motion a final common mechanism to produce identical disease patterns. Therefore, in order to best evaluate all the factors that may be operative in pneumatosis, a table of unselected cases of pneumatosis in infancy reported in the literature was drawn up and incorporated in this paper in an attempt to discover any denominator or denominators common to them all which may shed some light on the matter. In all likelihood this does not represent a complete list of all the cases reported in the literature, but undoubtedly it is a representative one.

Examination of Table I reveals the striking fact that although the initiating symptoms may be either respiratory or gastrointestinal, they all display either an acute enteritis or enterocolitis at autopsy, with or without an associated acute mesenteric lymphadenitis. It will be noted that in the autopsy diagnoses offered in the cases of Botsford and Krakower,[5] and in those of Lindsay and asso-

ciates,[6] no such diagnoses of enteritis or enterocolitis are forthcoming. However, in the microscopic descriptions of the bowels of these cases, the authors describe in each instance a mucosal acute inflammatory infiltrate of varying severity indicative of an acute enteritis. To further substantiate the presence of an acute enteritis, five of the six cases reported by Botsford and Krakower had an acute mesenteric lymphadenitis as well.

Further examination of Table I discloses that, as in the case presented in this paper, epithelial ulceration is not an invariable or n e c e s s a r y concomitant of pneumatosis. Of course, where ulceration does exist, its importance as a possible portal of entry for gas in the production of pneumatosis cannot be easily gainsaid. However, a serious doubt concerning its effectiveness as such must be raised in the light of the fact that, although ulcerative lesions of the bowel are of fairly frequent occurrence, pneumatosis is extremely rare. Moreover, no case of diastatic ulcer of the colon associated with pneumatosis has ever been reported, even in the presence of the considerable intraluminal gas pressure which is invariably associated with this condition. In addition, to further bear out the impression that a simple mechanical ulceration alone cannot operate to produce gas cysts, the experimental attempts of Tung and Ngai[7] to produce gas cysts in dogs by injecting air into the bowel wall ended in failure, although they did observe the passage of air into the mesenteric lymphatics. All this, together with the absence of epithelial ulceration in many cases of pneumatosis, introduces the possibility of another but still intangible factor that may be operating—that of altered mucosal permeability to gas—which produces a functional rather than a mechanical gap in the integrity of the epithelial barrier. For instance, Biester and co-workers,[8] in working on pneumatosis in swine, a condition bearing a great similarity if not identity with that in infants, demonstrated, in swine at least, that pneumatosis results from a dietary deficiency. They were able to induce the condition in a significant number of animals by feeding them solely a diet of polished rice and to protect them from cyst formation to some degree by a diet of unpolished rice, whole corn, and skimmed milk powder. Moreover, they concluded from their work (and this may have a bearing on the sporadic occurrence of pneumatosis in infancy) that there "appeared to be a definite individual variation in the susceptibility of different individuals to intestinal emphysema."[9] This is not to say, by analogy, that a dietary deficiency is an essential cause of pneumatosis in infants—although in adults as well as in the case presented here it may very well be a factor—but rather to point out the very real possibility of a functional disturbance acting as a competent producing agent of the disease, and to emphasize that a mechanical break in the integrity of the intestinal epithelium is not an absolute necessity. Curiously enough, pneumatosis of swine is always associated with a catarrhal enteritis. In infants, the bacterial infection itself rather than a dietary deficiency may be responsible for altering mucosal permeability to gas, although it is more likely that the latter may be a result of bacterial infection plus some factor as yet un-

known. Of course, as an interesting possibility, it is not inconceivable that imperceptible gas absorption is a normal bowel function, and only pathologic when it is excessive.

Referring to the table again, it will be noted that the age range of pneumatosis is from 2 weeks to 14 months. This may reflect either the greater susceptibility of infants to bowel infections than of any other age group, or a factor that Biester and associates[5] observed to be operative in swine. They observed that pneumatosis could be produced in swine placed on a diet of polished rice only when the swine were in a period of rapid growth, hence, we may have an analogous situation here, where the greatest incidence of pneumatosis may be expected to occur during periods of rapid growth, such as infancy. Superficially, this may seem to be at variance with the observed fact that the peak of greatest incidence of pneumatosis is in middle age. However, as will be elaborated further on, it is not at all improbable that in some, if not all, instances the disease in adults may have had its onset during a period of life much earlier than is apparent from its time of discovery.

A survey of the literature reveals that although pneumatosis in adults has been demonstrated unequivocally on more than one occasion to be a reversible process, such is not the case in infants, at least not until the case report submitted in this paper. Here, the discovery of pneumatosis of the small and large bowel at laparotomy and its complete disappearance from the colon five days later at autopsy is not only indisputable evidence that pneumatosis in infancy is not a terminal situation, as is sometimes claimed, but is undeniably a reversible condition as well. It is true that Stiennon[2] at an earlier date reported the reversibility of this process in his two cases. However, several objections may be raised in this regard, based on the tenuous nature of his observations which place the validity of his conclusions upon s h a k y foundations. First, although both of Stiennon's cases w e r e diagnosed roentgenologically, only one was confirmed by laparotomy and then by autopsy. And, second, although reversibility was concluded from roentgenologic evidence alone, autopsy disclosed the gas cysts still to be present in his first case. Thus, assuming that the correct diagnosis was made radiographically in the second case, which was not autopsied, the validity of the interpretation of reversibility from x-ray changes is certainly open to question in this case as well.

It is not meant to infer that pneumatosis of infancy cannot be diagnosed ante-laparatomy or ante-mortem from x-ray findings. In fact, as pointed out by Stiennon, the x-ray picture is so characteristic as to be specifically diagnostic; this was demonstrated not only in Stiennon's two cases but in the case presented here, which was diagnosed radiographically two days before verification at laparotomy. However, the interpretation of apparent disappearance of these radiographic changes as indicative of the disappearance of the gas cysts, as assumed by Stiennon, is open to question and is of dubious value, if any at all. Thus, although the presence of a double contour line to the bowel wall may be considered roentgenologically specific for pneumatosis, its disappear-

TABLE I. CASES OF PNEUMATOSIS

AUTHOR	AGE	SEX	SYMPTOMS	PORTIONS OF BOWEL INVOLVED BY CYSTS
Maas	7 mo.	M	Case incompletely worked up. Infant initially treated for chylous ascites of unknown cause	
Moore	9 wk.	F	Diarrhea	Jejunum and ileum
	14 mo.	F	Vomiting and diarrhea	Small bowel and colon
	6 wk.	M	Failure to gain weight and intermittent vomiting	Jejunum and ileum
	2 wk.	F	Diarrhea and skin eruption	Colon
Botsford and Krakower*	4 wk.	M	Failure to gain weight, cyanosis and pneumonia	Descending colon
	9 mo.	M	Edema and upper respiratory tract infection followed by vomiting and diarrhea	Ileum, ascending and pelvic colon
	7 mo.	M	Cough, cyanosis, pneumonia, vomiting and diarrhea	Ileum
	2½ mo.	M	Jaundice, vomiting and diarrhea	Jejunum
	3½ mo.	M	Vomiting and diarrhea	Ileum
	2 wk.	M	Blisters of hands, feet and body Intermittent diarrhea and vomiting	Colon
Lindsay, Rice, and Selinger	7 mo.	F	Rhinitis and diarrhea	Terminal ileum and ascending colon
Judge, Cassidy, and Rice	6 cases, 1 mo. 5 cases, 2 mo. 3 cases, 4 mo. 2 cases, 6 mo. 1 case, 8 mo.	10 M 7 F	Diarrhea was present in majority of cases. 15 cases had respiratory tract infection during some stage of their illness. Remaining 2 cases had severe infectious diarrhea	Ileum—12 cases Jejunum—5 cases Cecum—10 cases Ascending colon—7 cases Transverse colon—2 cases Descending colon—1 case
Autopsied by Captain P. T. Flynn (Brooke Army Hospital) Unreported	1 yr.	F	Vomiting and diarrhea	Terminal ileum, cecum, and ascending colon
Stiennon	4 wk.	M	Diarrhea and anorexia	Small bowel
	5 wk.	Not stated	Esophageal atresia and tracheobronchial fistula. Bloody diarrhea and regurgitation through gastrostomy	Diagnosed radio

*Although a diagnosis of enteritis is not included in the anatomic diagnosis of Botsford and Krakower's first five cases, these authors describe an acute inflammatory infiltration of the wall of the small bowel of these cases of mild to moderate severity.

CYSTOIDES INTESTINALIS REVIEWED

LOCALIZATION OF CYSTS WITHIN BOWEL WALL	OTHER SITES INVOLVED BY CYSTS	MICROSCOPIC FEATURES	MAJOR ANATOMIC DIAGNOSES
Mucosa, submucosa and serosa	—	Acute mesenteric lymphadenitis	Hemorrhagic enteritis
Mucosa and submucosa	—	Acute mesenteric lymphadenitis	Acute catarrhal enterocolitis
Submucosa and serosa	—	Acute mesenteric lymphadenitis Ulcer in ileum	Acute hemorrhagic enteritis
Submucosa, mucosa and serosa	—	—	Acute catarrhal enteritis and pemphigus
Mucosa and submucosa	—	No epithelial ulceration	Acute suppurative bronchopneumonia
Mucosa, submucosa and serosa	Mesenteric lymph nodes, cisterna chyli, and thoracic duct	Acute mesenteric lymphadenitis No epithelial ulceration	Subacute glomerulonephritis, bronchopneumonia, and mild nonobstructive biliary cirrhosis
Submucosa	Mesenteric lymph nodes	Acute mesenteric lymphadenitis Epithelial ulceration present	Bronchopneumonia
Submucosa	Mesenteric lymph nodes	Acute mesenteric lymphadenitis No epithelial ulceration	Mild nonobstructive biliary cirrhosis, mild rickets, and mild scurvy
Submucosa	—	Acute mesenteric lymphadenitis No epithelial ulceration	Mild nonobstructive biliary cirrhosis and mild bronchopneumonia
Submucosa and serosa	—	Acute mesenteric lymphadenitis No epithelial ulceration	Epidermolysis bullosa, bronchopneumonia, and acute enteritis
Not stated	—	Enteritis	Congenital syphilis
Not stated	Mesentery of upper part of ileum	Not stated	13 cases had ulcerative ileocolitis while 4 had various stages of ileocolitis
Mucosa, submucosa and subserosa	Mesentery and mesenteric lymph nodes	Epithelial ulceration present. Chronic hyperplastic lymphadenitis	Acute ulcerative enterocolitis
Submucosa	Transverse mesocolon and small bowel mesentery	Epithelial ulceration present	Lobar pneumonia, multiple old pulmonary infarcts, infarcts of small bowel, purulent peritonitis and chronic catarrhal colitis

graphically. Autopsy not performed

ance or absence has no positive significance whatsoever. Therefore, although it is anticipated that more frequent flat plates of the abdomens of infants may detect more cases of pneumatosis, a negative x-ray does not positively exclude the disease.

Further analysis of the cases enumerated in the table elicits the information that pneumatosis occurs more frequently in males than in females, with an approximate ratio of two to one. In addition, the cysts involve both small and large bowel indiscriminately, localizing in the mucosa, submucosa, and subserosa with, as pointed out earlier by Moore,[10] the mucosa and submucosa predominating. This latter feature of the disease in infancy has led some authors, notably Stiennon,[2] to conclude erroneously that intestinal obstruction commonly results from such localization of the gas cysts within the submucosa. That such is not the case is amply borne out by examination of the cases reviewed in this paper. It will be noted that none exhibit any evidence of intestinal obstruction directly attributable to gas cysts, and that even Stiennon's first case, although interpreted as such, is certainly open to question.

Another interesting feature of the gas cysts in infancy is that they are associated with little, if any, neutrophilic reaction in the contiguous stroma, the little that is present being easily accounted for on the basis of the mechanical factor of stretch. This would seem to indicate that the presence of gas in the intestinal lymphatics is essentially a bland process and induces no inflammatory reaction per se. Of course, this does not exclude the possibility that with either prolonged or increased pressure within the lymphatics injury to the lining endothelium will result and inflammatory reaction ensue. Indeed, Moore[10] observed an occasional giant cell in three of his cases, an unusual phenomenon in gas cysts of infancy, but only in association with fibrosis and fibrin deposits. And, curiously enough, Koss,[1] in his extensive review of pneumatosis in adults, noted that giant cells appeared with progressive fibrosis of the cysts. Here we have an apparent anatomic link between the lesions in infancy and those in adulthood.

Finally, if there is any doubt that the gas cysts in pneumatosis represent lymphatic channels distended with gas, it should be dispelled quickly by a survey of the cases reported in the literature. Thus, the fact that the gas cysts are described as being lined by an endothelium is suggestive enough that they are dilated lymph channels; but should further evidence be desired then certainly the presence of gas cysts within the mesenteric lymph nodes as well, in many of the cases, is not to be lightly overlooked. Moreover, it will be noted from Table I that Botsford and Krakower's[5] second case contained, in addition to the usual gas cysts within the small and large bowel and mesenteric lymph nodes, considerable gas within the cisterna chyli and thoracic duct. Further support is added by the predilection of the gas cysts in adults for the mesenteric border of the intestine[2] where there is a natural confluence of the intestinal lymphatics on their way to the mesenteric lymph nodes. Referring to pneumatosis in swine again, Eveleth and Biester[9] ob-

served, and this is probably applicable to pneumatosis in human beings as well, that the mesenteric lymph nodes are involved in advanced cases.

A THEORY OF PATHOGENESIS

From the foregoing case report and discussion several generalizations can be made which when assembled into some sort of order can give us some insight into the mechanism whereby the lesions of pneumatosis in both infants and adults develop. These generalizations are as follows:

1. The gas is localized within the lymphatic channels of the intestine and the presence of giant cells is indicative of chronicity.
2. Intestinal infection is always present in pneumatosis of infancy.
3. Epithelial ulceration is not necessary for the development of the lesions of pneumatosis of infancy and probably not operative at all even when present.
4. Pneumatosis of infancy, like its adult counterpart, is a reversible process.

Using these observations, the following sequence of events is postulated. Initially, there is an enteritis of bacterial nature with considerable intraluminal gas production and alteration in mucosal permeability to gas. The latter may result from bacterial activity per se but in view of the extreme rarity of the disease some other as yet unknown factor acting in conjunction with infection is the more likely explanation. In any case, the gas soon enters the mucosa and its lymphatics and passes through the lymphatics of the submucosa and muscularis to reach the subserosal lymphatics. The almost complete absence of gas cysts from the muscularis may be accountable to the contractility and considerable tensile strength of the muscularis, so that gas only momentarily occupies the lymphatics within the muscularis and then is propelled rapidly by muscular contractions into the subserosal lymphatics. These same factors are probably operative in the muscularis mucosae as well, where gas cysts have rarely, if ever, been encountered. The gas then passes via the lymphatics of the mesenteric fat to enter the sinuses of the mesenteric lymph nodes. The latter probably act as a trapping mechanism, simultaneously allowing slow gas absorption or diffusion into the tissues, and slow imperceptible seepage of the gas into the cisterna chyli and thoracic duct to occur. In this way gas embolization as a complication of pneumatosis is prevented and gradual dissipation of the gas is accomplished.

The mechanism outlined above may account for the complete absence of gas cysts from the mucosa of the case presented, since the disease had been present at least seven days from the date of its diagnosis radiographically to the date of autopsy, allowing sufficient time to elapse for all the gas within the mucosal lymphatics to pass to those within the submucosa and subserosa as well as to the mesenteric lymph nodes. It also helps to explain the differences in distribution and microscopic appearance noted between the gas cysts of the adult and infantile varieties, with predominantly serosal localization in the former and predominantly mucosal and submucosal localization in the latter. The infantile variety is interpreted as repre-

senting an acute process of such fresh or recent origin that the majority of the gas cysts are more superficially situated, insufficient time having elapsed to allow passage of most of the gas to the subserosal lymphatics and imperceptible absorption or diffusion of the gas within the mucosal and submucosal lymphatics to occur. The adult variety, on the other hand, is regarded as the chronic counterpart of the disease, where the condition has been of considerable duration; at least sufficient time has elapsed for the gas within the mucosal and submucosal lymphatics to have caused a foreign body type of inflammatory reaction within the bordering tissue. That the gas cysts in the adult variety of pneumatosis should persist and disappear only very slowly may be attributed to a blockage of the lymphatics distal to them, of which the foreign body reaction may be a part.

This mechanism, in addition, explains the occasional mesenteric and mediastinal gas cyst reported in adults. Moreover, it implies that the onset of the disease in adults considerably antedates the time of its clinical detection—possibly some long-forgotten transient enteritis, typhlitis, or enterocolitis initiating the entire process. This may explain those cases in adults which are unassociated with any other disease and called, therefore, primary pneumatosis. Furthermore, the frequent localization of the cysts in adults in the ileocecal region may be explained on the same basis, inasmuch as inflammatory disease is not uncommon in this region. In the other large group of cases of pneumatosis in adulthood which is associated with stenosing peptic ulcer, the diet-restricting feature of the latter together with intestinal infection may be the combination of circumstances which triggers the mechanism.

Finally, it is inescapable and highly in order on the basis of the mechanism of pathogenesis outlined above that the terms "acute" and "chronic pneumatosis" be substituted for the terms "infantile" and "adult pneumatosis," respectively. This is particularly advisable inasmuch as three of the cases in infancy reported by Moore[10] showed an occasional giant cell and three cases of the adult type gleaned from the literature by Koss[1] were in an age range of 2 to 10 years. Thus we have a more logical situation when we make our terminology a function of the age of the lesions rather than of the age of the patient.

SUMMARY

A case of pneumatosis cystoides intestinalis associated with congenital megacolon is submitted, the first of its kind to be recorded in the literature.

A dynamic concept of the pathogenesis of pneumatosis is offered which accounts for both the infantile and adult varieties of the disease.

It is suggested that the terms "acute" and "chronic pneumatosis" be substituted for the terms "infantile" and "adult pneumatosis," respectively.

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MANAGEMENT OF HEMOPHILUS INFLUENZAE, TYPE B, MENINGITIS

Analysis of 128 Cases

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MANAGEMENT of acute purulent meningitis has been greatly modified during the past fifteen years. As the result of widespread application of antibacterial agents, steady decrease in mortality rate and incidence of complications has resulted. Seven hundred fifty-eight patients with meningitis have been studied and treated at the Los Angeles Childrens Hospital from 1930 to 1953. A detailed analysis revealed:

	CASES
1. Tuberculous	168
2. *Hemophilus influenzae*	128
3. Meningococcus	126
4. Pneumococcus	98
5. Miscellaneous	238

All cases of *H. influenzae* meningitis have been reviewed to evaluate results of varying therapeutic regimes. As indicated in Fig. 1, the absolute number of patients has steadily increased, undoubtedly reflecting not an actual increase in disease, but rather the result of increase in total patient load, as well as increase in staff interest. In keeping with experience of others, mortality rate before 1941 was 100 per cent, but since then the number of deaths has decreased, so that only two deaths were recorded from 1948 through 1953.

The peak months of incidence were March and November (Fig. 2), emphasizing the relationship to preceding respiratory infections. Ninety-nine (77 per cent) of this group had such an infection, with otitis media present in fifty cases. Bronchopneumonia was present in only eight, with no cases of croup or epiglottitis encountered. Concomitant disease was otherwise infrequent. Two patients had previously recognized congenital heart disease and one had diabetes mellitus.

Age and Sex.—Age distribution ranged from 7 weeks to 12 years (Fig. 3). Fifty patients were under 1 year of life, with the peak incidence between 7 and 9 months. Only 12 were over 6 years. Predilection for the young age group is well known and needs no further comment here. Seventy-six (60 per cent) of patients were males.

Race.—All children were Caucasian except 2 Negroes and 2 Orientals.

Course Before Hospitalization.—Duration of illness was from six hours to seven weeks. Meningeal symptoms were present less than twenty-four hours in seventy cases. Seventy-one received sulfonamides and/or antibiotics before admission. Thirty-six received penicillin.

Fever, vomiting, and lethargy were the most frequent complaints. Stiff neck was mentioned in sixteen histories, opisthotonus in four, and bulging anterior fontanel once. Convulsions occurred in twenty-seven patients.

Physical Findings.—Sixteen patients were afebrile on admission, ap-

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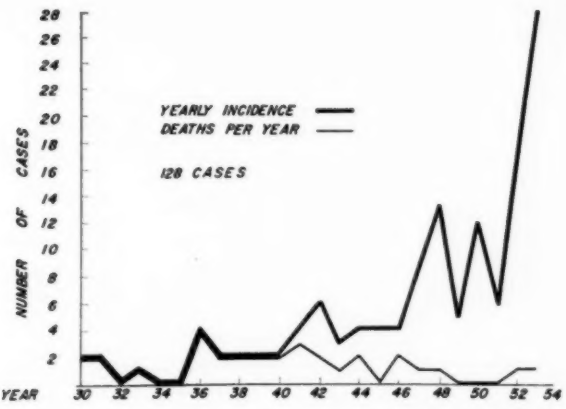

Fig. 1.—Number of cases of *Hemophilus influenzae* meningitis, with deaths, at Los Angeles Childrens Hospital. Review of 128 cases.

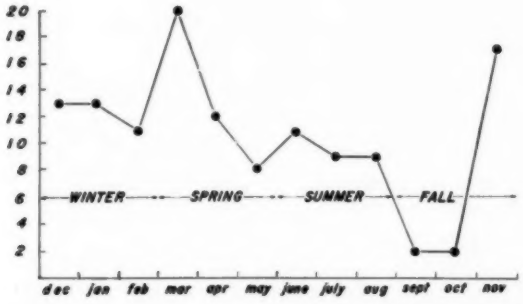

Fig. 2.—Seasonal incidence of *H. influenzae* meningitis as determined by analysis of 128 cases.

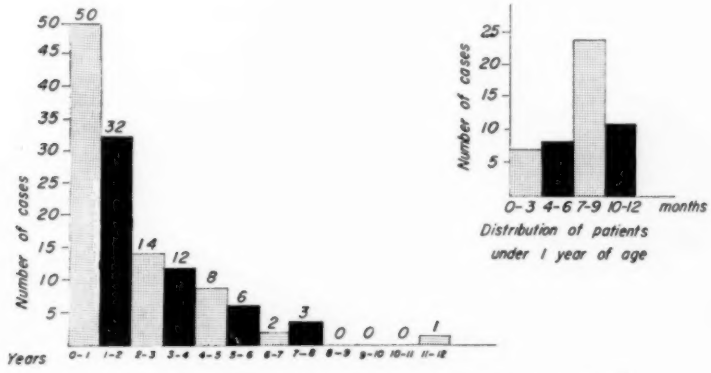

Fig. 3.—Age distribution of 128 cases of *H. influenzae* meningitis.

proximately one-half having previously received chemotherapy or antibiotics. There appeared no relationship between presence or absence of fever and age or clinical condition of patient.

Average temperature was between 102° and 105° F., with 107° F. maximum.

Ninety-seven (75 per cent) exhibited nuchal rigidity, with only forty-three having positive Kernig and Brudzinski signs. Thirty-one were admitted in a comatose condition and twelve in a moribund state. These latter children were the ones in which nuchal rigidity was absent. Cranial nerve abnormalities were rare. Facial nerve paralysis occurred in one, strabismus in five, ptosis in one, and papilledema in three. Frequency of respiratory illness has already been indicated. It is worthy of mention that *no petechiae* were noted in the skin or mucous membrane surfaces.

LABORATORY FINDINGS

Bacteriology.—Nasopharyngeal cultures were recorded in fifty-six patients and of these, *H. influenzae* was found in twenty-eight (50 per cent). Blood cultures drawn in seventy-four cases revealed fifty-three (71 per cent) positive for *H. influenzae*. Spinal fluid cultures were positive in 116 of 128 patients. Diagnosis was established in the remaining twelve cases by positive blood and nasopharyngeal cultures.

Blood.—Hemoglobin values varied from 6 to 15 grams, with fifty-three instances of values less than 10 grams. As these were primarily in the age group below 12 months, the reduced value was considered primarily due to iron deficiency rather than a specific result of infection. Total leukocyte counts ranged from 2,700 to 55,000 per cubic millimeter, with eighty patients having admission counts over 15,000 per cubic millimeter. Differential counts revealed a range of granulocytosis from 20 to 96 per cent. The lowest percentage of granulocytes accompanied the lowest total leukocyte counts but there appeared no relationship between level of leukocytes and mortality rate.

Spinal Fluid.—Cell counts were from 2 to 20,000 per cubic millimeter, with only thirteen patients having counts less than 500 cells per cubic millimeter. *H. influenzae* was cultured from the spinal fluid with the lowest cell count.

Differential cell counts usually revealed 80 to 100 per cent polymorphonuclear forms, although three patients exhibited a 70 to 90 per cent lymphocytosis. These patients had received previous partial treatment.

Sugar values ranged from 5 to 100 mg. per cent and appeared to have no constant relationship to mortality. Protein values were elevated above 30 mg. per cent in 112 patients. In general, the lower cell counts usually correlated with lowest protein and highest sugar content.

Direct identification of the organism by smear and Gram's stain and/or quellung reaction proved correct in 75 per cent of 106 cases thus studied. The most common error was inability to differentiate *H. influenzae* from meningococci with the Gram's stain technique.

Studies of bacterial sensitivity have been carried out during the past few years, employing the disk method. All

organisms except one so studied were found sensitive to oxytetracycline, chloramphenicol, and streptomycin. In this one instance, in vitro, moderate resistance was shown to oxytetracycline. However, the patient was treated with the combination of sulfonamide, streptomycin, and oxytetracycline with prompt, complete recovery.

RESULTS OF TREATMENT

Evaluation of therapy is outlined in Fig. 4. The first fourteen patients, receiving only supportive measures, all died within two weeks of admission to the hospital. They all maintained a septic temperature course (102° to 104° F.), vomited frequently, fed poorly, became progressively more spastic and lethargic, and had frequent convulsions. Daily spinal drainage afforded relief until block occurred, usually followed by death within forty to seventy-two hours. Terminal pneumonia and mastoiditis were frequent findings at autopsy. There were no survivors in this group.

The second group of thirteen patients treated with sulfonamide alone had two survivors, a mortality rate of 85 per cent. Following institution of treatment the course was more prolonged, with some patients surviving 1 to 2 months. Cerebrospinal fluid cultures usually remained positive. Sulfonamide was used in amounts up to 0.4 gram per kilogram of body weight, with frequent complications of methemoglobinemia, hematuria, and one case of agranulocytosis. The two survivors recovered rapidly, becoming afebrile within two to three days, with no residual complications.

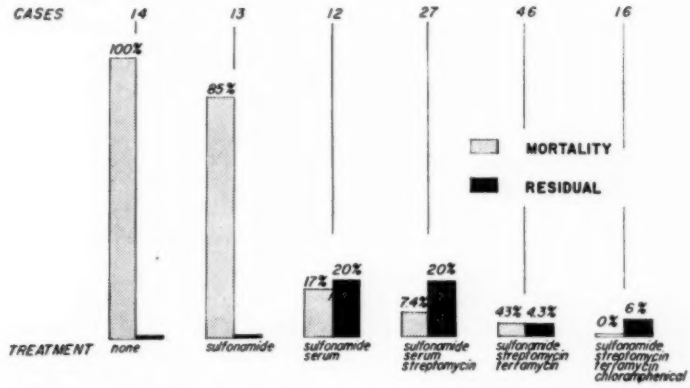

Fig. 4.—Analysis of 128 cases of *H. influenzae*, type B, meningitis showing steady reduction of mortality and residual complications with improving methods of treatment.

The combination of sulfonamide plus Alexander's rabbit antiserum was employed in twelve patients, with two deaths, a mortality rate of 17 per cent. Residuals of mental retardation, blindness, hydrocephalus, and convulsions occurred in 20 per cent of survivors. Hospitalization averaged four to five weeks.

In 1946, streptomycin was introduced, and in twenty-seven patients the combination of sulfonamide, streptomycin, and rabbit antiserum

(six patients) resulted in a mortality rate of 7.4 per cent. In spite of this improvement, the incidence of residuals was 20 per cent, with hydrocephalus, convulsive disorders, mental retardation, and deafness. Recurrences were noted in two patients (7.4 per cent). The average length of hospitalization was three weeks.

Oxytetracycline was first used here in 1949, and the group of patients receiving it in combination with streptomycin and sulfonamide comprise the largest series, fourty-six. The mortality rate was 4.3 per cent (two deaths) and the incidence of residual complication was also 4.3 per cent. Hospitalization averaged two to three weeks and there were no relapses.

Chloramphenicol has not been routinely used but the last group of sixteen patients with no deaths received this drug in various combinations with others. This is a particularly difficult group to evaluate as no overall single plan was utilized. Three were initially started on this; two in combination with streptomycin and sulfonamides, and one with Terramycin added to the previous combination. These did well without complications. Eight were initially treated with various combinations of streptomycin, sulfonamides, oxytetracycline, and/or Aureomycin with favorable clinical and laboratory response. Chloramphenicol was introduced later but seemed to contribute nothing to the already favorable recovery. The final five cases were the most complicated and clear evaluation is difficult. For this reason, a brief abstract of each case is presented.

CASE 1.—C. S., a 10-month-old Mexican male, was admitted with a three-week history of cough and coryza, and three days of fever associated with vomiting and irritability. He was critically ill. Fine inspiratory râles with dullness were noted at the right base. No meningeal signs were noted and the cerebrospinal fluid was clear. Blood and nasopharyngeal cultures grew out *H. influenzae*, type B. Therapy was started with aqueous penicillin and Gantrisin. With the culture report, therapy was switched to intravenous oxytetracycline, 50 mg. per kilogram daily, and penicillin and Gantrisin were discontinued. The child improved, became afebrile, and after two days of intravenous therapy was switched to oral oxytetracycline in the same dosage. During the next three days he remained afebrile, but was very irritable, arched his back, and vomited intermittently. One week after admission he again became febrile and repeat cerebrospinal fluid study revealed turbid fluid with 460 cells per cubic millimeter, 88 per cent polymorphonuclears. The blood, nasopharyngeal, and cerebrospinal fluid cultures were negative. At this point chloramphenicol and streptomycin were added to the therapy, and he made an uneventful recovery.

CASE 2.—J. R., an 8-month-old white male, was admitted with a four-day history of fever, with a left-sided convulsion on the day of admission. He had received penicillin and Aureomycin (amount unknown) three days before admission. On admission he was convulsing, and the anterior fontanel was bulging. Cerebrospinal fluid was purulent and *H. influenzae*, type B, was cultured. The infant was started on Aureomycin, 20 mg. per kilogram daily, intravenously, and streptomycin, 0.5 Gm. daily. He remained febrile for the next five days but clinically improved and began to take formula. Repeat cerebrospinal fluid unfortunately was bloody. Because of the uncertainty, due to the bloody tap and persistent

fever, the patient was switched to chloramphenicol, became afebrile within twelve hours, and made an uneventful recovery.

CASE 3.—R. K., an 8-month-old white male, was admitted with a one-week history of coryza, fever, and irritability for three days. Two days before admission he was given intramuscular penicillin and oral oxytetracycline (dosage unknown). He became severely ill on the day of admission and had a generalized convulsion. On physical examination the baby appeared moribund and in circulatory collapse. Blood pressure was 30/0, pulse 180, respirations were gasping, and the temperature was 39° C. The skin was mottled and cyanotic. The anterior fontanel was tense and bulging. The blood and cerebrospinal fluid cultured *H. influenzae*, type B, and the spinal fluid cell count was 8,000 per cubic millimeter, 92 per cent polymorphonuclears. The infant was started on intravenous oxytetracycline, 50 mg. per kilogram daily, together with sulfadiazine, streptomycin, and routine supportive measures. He made an initial good response. Five days after admission, the spinal fluid cell count was 220 per cubic millimeter. Because of persistent fever, subdural taps were done on the sixth day and bilateral effusions discovered. These were difficult to manage by repeated needle aspiration so that surgical drainage was required. The right subdural space continued to yield fluid for two more weeks. Low-grade fever persisted throughout this period, and because of this intramuscular chloramphenicol was begun even though the cerebrospinal fluid was clear. The baby remained febrile and one week later a scalp wound infection became evident and was drained. Thereafter he became afebrile and made an uneventful recovery, being hospitalized for a total period of six weeks.

CASE 4.—E. R., a 6-month-old white male with a two-week history of respiratory infection, acute onset of fever and bulging fontanel for twenty-four hours. The cerebrospinal fluid contained 1,020 cells per cubic millimeter. Initial daily therapy was intravenous oxytetracycline, 100 mg. per kilogram, streptomycin 50 mg. per kilogram, and sulfadiazine, 0.3 Gm. per kilogram. Because of initial rapid clinical improvement, he was switched to oral Terramycin after two days of intravenous therapy. After twenty-four hours his temperature rose to 40° C. Spinal fluid was bloody. On the seventh day of therapy the white blood count had dropped to 6,350 and a rash similar to roseola appeared. He then became afebrile but continued to vomit intermittently. Subdural taps were dry. Two weeks after admission the cerebrospinal fluid still showed 250 cells per cubic millimeter, and he was started on oral chloramphenicol, 100 mg. per kilogram daily, and oxytetracycline discontinued. One week later he again became febrile and a repeat cerebrospinal fluid examination revealed 1,000 cells with 75 per cent polymorphonuclears and a negative culture. At this point oxytetracycline was again added to the therapy and the infant went on to an uneventful recovery. Follow-up shows no neurological residual.

CASE 5.—J. D. was a 2½-year-old white male with a ten-day history of a cold with intermittent earaches. On the day of admission he became febrile and stuperous. Cerebrospinal fluid examination showed 8,000 cells per cubic millimeter, chiefly polymorphonuclears. He was started on intramuscular oxytetracycline, 100 mg. per kilogram, streptomycin, 1 Gm. daily, and Gantrisin, 0.25 Gm. per kilogram daily. Two weeks after admission he still maintained a low-grade fever in spite of a clearing spinal fluid. He was noted to be ataxic, and x-rays of the skull showed diastasis of the cranial sutures. Chloramphenicol therapy was begun. The patient remained febrile for one additional week and then began to steadily improve. He was discharged

from the hospital six weeks after admission in good condition except for a mild ataxia.

In Cases 1 and 2, initial therapy was not as intensive as is now recommended nor in the same combination. Patient 3 made a good initial response but subdural collections of bloody fluid were found on the sixth day, and later a scalp infection was an added complication. After eradication of this, the course was uneventful. It seems highly improbable that chloramphenicol contributed anything to control of the original infection, but probably was of value in helping eliminate the hemolytic staphylococcus scalp infection.

In Case 4, therapy was decreased very rapidly, beginning the second day of treatment, and vomiting of oral medication undoubtedly resulted in low oxytetracycline body fluid levels. Although there was definite improvement, the patient did not become completely well and chloramphenicol was substituted on the fourteenth day, followed by a clinical relapse, apparently controlled by addition of oxytetracycline to chloramphenicol. Patient 5 made a good initial response to the usual therapy and was never seriously ill after the first three days of hospitalization. His recovery was gradual over a three-week period. After two weeks, chloramphenicol was substituted for oxytetracycline without dramatic change in the patients' course, but eventual recovery.

In summary of this last group, we do not believe chloramphenicol has appeared to add anything to our usual form of therapy. In the literature[1-6] seventy-five cases are reported in which the patients were treated with chloramphenicol alone or in combination with sulfadiazine. Three deaths were reported (4.0 per cent), with six cases (8.3 per cent) showing residual complications and fourteen subdural effusions. No hematologic abnormalities were noted although these have been noted elsewhere.[7-10] Evidence is accumulating that chloramphenicol can produce hematopoietic damage[11-18] and its use should be attended with very close observation. In view of this potential danger, and lack of demonstrated superiority over oxytetracycline, we have preferred the latter in the routine plan of management.

Frequent occurrence of subdural effusions and hemorrhage secondary to meningitis has been emphasized.[19, 20] During the past two years subdural taps have been done in any child whose clinical symptoms suggested this possibility. Twenty-one patients were investigated in this manner, with positive findings in eight. Prior to this time, one additional effusion was found at autopsy in a child treated by sulfonamide alone. Six of the eight effusions disappeared with repeated needle aspirations. One patient required craniotomy with removal of a membrane, and one responded to surgical exploration with irrigation of the subdural space.

The two deaths occurring from 1948 through 1953 are worthy of more detailed comment.

A 3-month-old white male was admitted in November, 1952, in a moribund condition, surviving only thirty-six hours. His course was stormy and septic with convulsions and death in spite of vigorous specific and supportive treatment. Unfortunately no autopsy could be obtained.

The second patient was a 2-year-old white girl admitted in August, 1953. She became afebrile on the second day of combined therapy with sulfonamides, streptomycin, and oxytetracycline. There was marked clinical improvement with clearing of cerebrospinal fluid and normal blood findings until the eighth day, when she suddenly again became febrile with leukocytosis of 30,000 per cubic millimeter. Cyanosis, circulatory collapse, and shock developed the following day. Supportive measures failed and death occurred two days later. Blood cultures revealed hemolytic *Staphylococcus aureus,* also grown from the spleen, bowel, and respiratory tract at autopsy. This organism was found to be extremely resistant to all antibiotics.

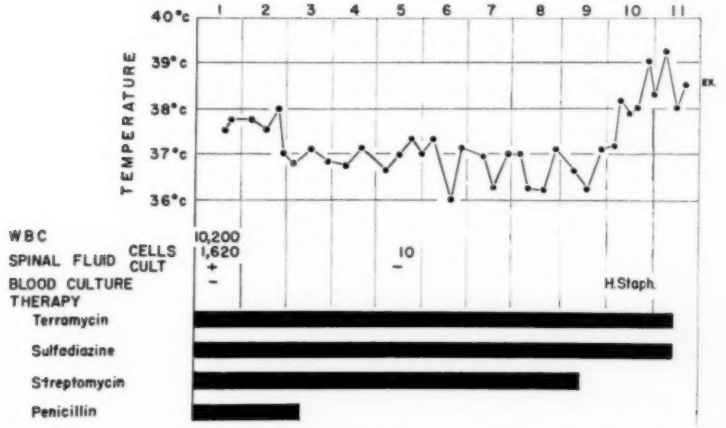

Fig. 5.—Clinical course of patient cured of meningitis but dying with complication of terminal hemolytic staphylococcus sepsis.

DISCUSSION

In view of the relatively small number of patients treated in certain of our categories, it is realized that the established figures cannot be too closely compared. However, certain very definite trends and results seem evident.

Slight improvement (15 per cent) in survival rate (Fig. 4) with use of sulfonamides alone (over no specific treatment) has been reported previously. Introduction of specific rabbit antiserum plus sulfonamides achieved 83 per cent survival rate. With increased survivals, complications due to cerebral damage became more evident, amounting to 20 per cent. Addition of streptomycin to the previous combination further increased survivals to 92.6 per cent and was also attended by residuals amounting to 20 per cent. Since combined use of oxytetracycline, streptomycin, sulfonamides (and frequently chloramphenicol), survivals have increased to 96.8 per cent with only 5 per cent complications.

Much has been written regarding best use of antibiotics and sulfonamides in this condition. Sulfadiazine has proved slightly effective against *H. influenzae* and in itself is not the drug of choice. Several antibiotics

are more efficacious: streptomycin, Chloromycetin, Terramycin, Aureomycin, and Achromycin.

Choice of therapeutic agents is based on ability to satisfy the following important considerations: (1) The agent must be rapidly effective against the organism in concentrations not toxic to body tissues. (2) It must permeate the intraspinal space in adequate concentrations. (3) A satisfactory parenteral preparation is necessary. (4) A combination of drugs with different modes of action on bacteria is desirable to reduce emergence of bacterial resistance.

Sulfadiazine meets the above criteria. It may be given subcutaneously as the sodium salt, in 0.5 to 5.0 per cent concentration, in ⅙ molar sodium lactate or lactate Ringer's solution. Usually twelve-hour dosage of 0.1 Gm. per kilogram is adequate to maintain plasma levels of approximately 15 mg. per cent. Diffusion into the spinal fluid results in levels approximately 60 per cent of those in plasma. If the urine pH is maintained at 7.0 to 8.0, renal complications are unlikely. This is easily accomplished by administering the equivalent of 3 to 5 c.c. molar sodium lactate (18 to 30 c.c. ⅙ molar) per kilogram of body weight daily. Subcutaneous administration should be continued for two to three days. If the clinical course is satisfactory and without vomiting, oral triple sulfonamides may be substituted, and continued for approximately one week. Alexander and associates[21, 22] have demonstrated delay in emergence of bacterial resistance to streptomycin through simultaneous use of sulfadiazine.

Streptomycin is very efficacious, bactericidal in concentrations of 10 mg. per cubic centimeter.[23] It may be given subcutaneously or intramuscularly, readily diffusing into the cerebrospinal fluid. Daily dosage of 50 mg. per kilogram is used. The mode of action differs from sulfonamides[24] and tetracycline[25] drugs. As maximal bactericidal effect and increasing bacterial resistance both occur rapidly, streptomycin is usually discontinued on the fourth day. Vestibular damage has been cited by Alexander[24] as occurring only twenty-four hours following intramuscular use of streptomycin, plus one intrathecal injection. During the last five years, in our patients, streptomycin has been given only subcutaneously or intramuscularly, and only one patient developed evidence of mild vestibular damage which has steadily improved. Here there is no assurance this was due to streptomycin as it could have resulted from the meningitis itself.

H. influenzae, type B, is known to be very sensitive to oxytetracycline which acts differently from the above-mentioned drugs. During the first one to three days' therapy, it is given intravenously in daily amounts of 100 mg. per kilogram of body weight, divided into equal doses every six hours. Dependent on the clinical condition, intramuscular or oral preparations are then substituted. In favorable cases, this is continued for ten to fourteen days, with gradually decreasing dosage.

Control patients without meningitis ordinarily show very low cerebrospinal fluid concentrations of oxytetracycline compared with plasma levels in patients with meningitis. However, we have commonly found

cerebrospinal fluid levels of 2.5 to 5.0 μg with simultaneous plasma levels of 10 to 40 μg. Most strains of *H. influenzae*, type B, respond to in vitro concentrations of 0.01 to 0.5 μg., which is easily achieved. Evidences of toxicity have been slight, with infrequent nausea, vomiting, and diarrhea. The most striking change since introduction of this drug has been the marked reduction in complications. Although the mortality rate was reduced from 7.4 per cent in the preceding group to 4.3 per cent, the residual complications in survivors has decreased from 20 to 4.3 per cent. Recovery has usually been prompt, with usual disappearance of fever within three to five days. No hematologic complications have been noted.

Use of multiple agents as applied in our series, has been done with realization of the possibility of antibiotic antagonism as described by Jawetz and co-workers[26, 29] in their laboratory, utilizing in vitro and in vivo studies. Emphasis must be placed on the minimal doses necessary to produce this phenomenon and the fact that it cannot be shown when therapeutic amounts are used. Clinically, only the study by Lepper and Dowling[30] would seem to bear out this possibility, while that of Ahern and associates[31, 32] failed to demonstrate such antagonism between penicillin and Aureomycin, and penicillin and chloramphenicol. In our cases, penicillin was sometimes administered for twenty-four to thirty-six hours before definite bacterial identification, and in no case was there evidence these children did less well than others not similarly treated. There seems no adequate reason now to not utilize antibiotic combinations, and indeed recent work[33, 34] has emphasized the possible importance of combinations of antibiotics in delaying emergence of bacterial resistance.

A very disturbing complication of antibiotic therapy is manifest in the second death in our last sixty-three patients. This child had entirely recovered from meningitis (Fig. 5) only to succumb to overwhelming resistant hemolytic staphylococcal sepsis on the eleventh day. Superimposed infection occurring during antimicrobial therapy has been increasingly noted.[35, 36] Alterations in normal bacterial flora of the respiratory and gastrointestinal tract; tissue alterations, as enterocolitis; increasing numbers of resistant bacteria (especially hemolytic staphylococcus) in hospitals; and possible stimulation of bacterial growth by antibiotics, are all possible factors. Whatever the reasons we must be increasingly alert to this danger.

SUMMARY

1. Detailed analysis has been made of 128 patients with meningitis due to *H. influenzae*, type B, treated at the Los Angeles Childrens Hospital.

2. Steady reduction in mortality rate and incidence of complications has been achieved, with two deaths in the last sixty-two patients (3.2 per cent mortality) and 5 per cent residual complications.

3. Standard plan of therapy is outlined, using a combination of sulfonamides, streptomycin, and oxytetracycline.

4. Subdural effusions were known to be present in eight patients during life. Six cleared with repeated taps, one with surgical irrigation, and one

required removal of membrane. An additional subdural effusion was found at autopsy. Subdural taps should probably only be done for specific cause and not routinely.

5. Adrenal steroid therapy was not used.

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ELECTROCARDIOGRAPHIC CHANGES DURING THE COURSE OF MEASLES

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ALTHOUGH it has become increasingly evident that myocarditis is a not infrequent concomitant to many of the common acute infectious diseases, there is little definitive information available in the case of measles. It is the purpose of this paper to describe the incidence and character of electrocardiographic changes during the course of this disease.

As early as 1912[1, 2] an etiological relationship was suggested between measles and cardiac affections. A 3-year-old child was described, who, fourteen days after the onset of measles, developed complete heart block which disappeared three weeks later. Since digitalis had been given for some unspecified reason for three days preceding the event, and since the measles was complicated by influenza, the postulated relationship must be considered doubtful. Twelve years later, Scham[3] listed three instances of severe arrhythmias associated with measles, one of which was the case previously cited. The two others were (a) recurrent complete heart block with an alleged ventricular rate of 260 with recovery, and (b) complete heart block lasting three to four years, listed as questionably associated with measles. No further details were given. Two patients with asymptomatic heart block described by Bower[4] gave a history of having had severe measles eleven and sixteen years previously.

A study of serial electrocardiograms during the course of measles was first reported by Neubauer,[5] who demonstrated changes in all four patients so studied. All, however, suffered from a complicating pneumonia and manifested the changes only during the febrile period.

Three instances of heart block thought to be related to measles were described in 1948.[6] Two of the three patients undoubtedly had rheumatic carditis. The third was that of a 2-year-old boy who began to have seizures during an attack of measles, was first studied one year later, and finally succumbed two and one-half years after the onset during a Stokes-Adams attack.

Lyon[7, 8] described two cases in recent years. The first was a 41-year-old man who had right bundle branch block and who gave a history of first sensing arrhythmical beating during a bout of measles two years previously, with recurrent episodes of tachycardia in the interim. The second was a 27-year-old woman studied seventeen days after the onset of measles because of lassitude and slight precordial pain of five days'

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duration. The finding of an inverted T_{CF_2} was interpreted as indicating "myocardial damage due to measles and perhaps autonomous nervous imbalance." The isolated finding of an inverted T_{CF_2} in a five-lead electrocardiogram (Leads, I, II, III, CF_2 and CF_4 cannot be accepted as reliable evidence of myocarditis.

Of eight cases of measles studied carefully by physical examination and serial electrocardiograms,[9] six exhibited no abnormality, while two were thought to show borderline changes. Giustra and Nilsson[10] described a 5-year-old child who came to their attention thirteen days after the onset of measles, because of tachycardia, the origin of which was thought to be either ventricular or supraventricular, accompanied by bundle branch block. During the following three years,[11] there were numerous episodes of bizarre arrhythmias, supraventricular tachycardia, and conduction block, with death finally occurring during a convulsive seizure. Autopsy disclosed the existence of a subendocardial sclerosis and focal fibrosis in the left bundle branch, but no myocardial changes. Since the child had been followed from birth and had appeared to be normal until an attack of measles, the etiology of the lesion was attributed to the infectious process. The reported findings, however, are consistent with a diagnosis of subendocardial fibroelastosis.

A recent study[12] of seventy-one children with measles revealed a high incidence of electrocardiographic abnormalities. Thirty per cent of the patients had prolonged P-R intervals, 29 per cent showed prolonged QT_c values, and an R′ in Lead CF_2 was found in 28 per cent. Since only 105 electrocardiograms were taken, an average of only one and one-half per child, the interpretations were of necessity made by comparison with a table of normal values. Considering that standards for children are not as well defined as they are for adults, the interpretation of deviations from any set of standards is open to some doubt. Two-thirds of the patients with prolonged P-R interval, when compared with the standards of Ashman and Hull, were studied from one day to four months later. Only four demonstrated a change toward normal. It must be concluded, therefore, that either measles commonly produces a long-standing or permanent effect on auriculoventricular conduction, or that the standards of normality were too rigid.

Some of the papers cited above record the occurrence of cardiac abnormalities during measles but do not present sufficient evidence to establish a causal connection. The demonstration of a temporal relationship does not always indicate an etiological one. The onset of arrhythmias during or shortly after an attack of measles may be entirely fortuitous. Considering the fact that 95 per cent of people suffer from this disease at some time during their life, it is not inconceivable that instances of the concurrence of almost any other human illness can be found.

METHODS

One hundred six patients admitted to the Haynes Memorial Hospital with measles were the subjects of this study. An attempt was made to obtain electrocardiographic tracings

every other day during the period of hospitalization. This was done with variable success, the interval being longer than two days in some instances. Twenty-nine patients had only two electrocardiograms taken. All tracings were performed on supine subjects, and all except the very young had twelve lead electrocardiograms. In the latter, Leads V_3 and V_5 were omitted in many cases.

Criteria for definite abnormality of the P-R interval were (1) at least 0.04 second over the upper limit of normal for age and rate established by Ashman and Hull,[13] (2) a change of 0.03 second or more without a change in heart rate, and (3) an increase of 0.02 second or more with an increase in heart rate of over 20 per minute. Particular attention was given to the shape of the P waves to exclude a change in the location of the pacemaker as a cause of the changes in A-V conduction interval.

T-wave changes were considered significant only if there was marked lowering or inversion, in dependable leads, i.e., Leads I, aV_L, or the left precordial leads. Care was taken to eliminate the effects of changes in the electrical position of the heart. Cases were encountered in which there was sharp inversion of the right but not of the left precordial T waves. Subsequent records showed sharp inversion of mid- or even left precordial T waves, with later a return to the original pattern. Accompanying this change, there was a shift in the transitional zone of the QRS complex. The meaning of such alterations in the electrical position of the heart is not always clear, but they were not considered abnormal in this study.

The Q-T interval was carefully measured in all cases, but no conclusive abnormalities were found. Numerous other changes (sometimes listed as significant in other studies) were encountered, but were not considered pathological. Such findings as sinoauricular tachycardia, shifting auricular pacemaker, changing electrical axis, occasional ventricular premature beats, and slight ST-T changes were not considered as of even borderline significance.

RESULTS

A total of 395 electrocardiograms was made on 106 cases of measles, an average of 3.7 per patient. In forty-eight instances the infection was uncomplicated. Pneumonia was present in twenty-eight, five developed otitis media, encephalitis occurred in sixteen, and nine suffered from miscellaneous concurrent diseases. Twenty (19 per cent) were considered to have definite electrocardiographic abnormalities, while five (5 per cent) had changes which were considered border line and, therefore, were not included in the statistical analysis. With one exception, the abnormalities were limited to changes in the T waves or in the P-R interval. The exception was a 5-year-old child with measles encephalitis, who developed numerous auricular premature beats beginning sixteen days after admission and persisting for one week. Five previous electrocardiograms had been normal. Such auricular irritability is unusual in children and was thought to indicate involvement of the heart.

Two patients with right bundle branch block were encountered. A 6-year-old girl with uncomplicated measles had a delayed intrinsicoid deflection of 0.05 second on admission to the hospital. This persisted and was present twenty months later. This abnormality could not be attributed with any confidence to rubeola. The second patient was a 7-year-old boy with uncomplicated measles, whose intrinsicoid deflection on admission to the hospital was 0.04 second at a rate of 125 per minute. Subsequent tracings, taken when the heart rate was 60 to 90 per minute, revealed an intrinsicoid deflection of 0.02 second. It seems most likely that the aberrant conduction in this instance was a result of tachycardia and not associated with the rubeola per se.

tion of age could be drawn, however, because only 18 per cent of all the patients were older than 10 and only 7 per cent were over 20. No correlation could be established between the severity of the measles and the occurrence of electrocardiographic abnormalities.

Fever was present in only three of the twelve patients with T-wave changes; all with prolonged P-R intervals were afebrile when the abnormality was detectable. We are unaware of data concerning metabolic alterations during measles. Blood chemical determinations were not carried out routinely in the present investigation. Nevertheless, nineteen of the twenty patients with abnormal tracings were eating and drinking well at the time when electrocardiographic changes were demonstrable.

TABLE I

	CASES	CASES WITH ABNORMAL EKG							
		ABNORMAL T		ABNORMAL P-R		APB*		TOTAL ABNORMAL	
Uncomplicated	48	9		4		0		13	(27%)
Complicated	58	3		3		1		7	(12%)
Pneumonia	28	0		1†		0		1	(4%)
Encephalitis	16	3		2		1‡		6	(38%)
Otitis media	5	0		0		0		0	
Other	9	0		0		0		0	
Total	106	12	(11.3%)	7	(6.6%)	1	(0.94%)	20	(18.8%)

*Auricular premature beats.
†Pneumonia and laryngotracheobronchitis.
‡Encephalitis and otitis media.

Table I indicates that electrocardiographic abnormalities were encountered in 27 per cent of the uncomplicated and in 12 per cent of the complicated cases. No differences in sex distribution were apparent in those with normal and abnormal tracings. All seven instances of P-R prolongation occurred in children less than 10 years old, and nineteen of the twenty cases showing electrocardiographic changes were under 20. No conclusions concerning the relation of age could be drawn, however, because only 18 per cent of all the patients were older than 10 and only 7 per cent were over 20. No correlation could be established between the severity of the measles and the occurrence of electrocardiographic abnormalities.

Fever was present in only three of the twelve patients with T-wave changes; all with prolonged P-R intervals were afebrile when the abnormality was detectable. We are unaware of data concerning metabolic alterations during measles. Blood chemical determinations were not carried out routinely in the present investigation. Nevertheless, nineteen of the twenty patients with abnormal tracings were eating and drinking well at the time when electrocardiographic changes were demonstrable. It seemed unlikely, therefore, that these could be attributed to abnormalities in acid-base balance. Abnormal electrocardiograms were noted as early as two and as late as twenty days after the onset of the measles rash, 25 per cent occurring after ten days. The duration of the abnormality was less than one week in most instances, being as short as four days or less in many cases.

Since the presence of electrocardiographic abnormalities did not deter-

mine length of hospital stay, several patients were discharged before subsequent normal tracings were recorded. Most of these were seen about a year later when they were found to have normal electrocardiograms. Of the twenty patients who showed abnormal tracings, a normal one was obtained at some time during the period of study in eighteen. Thus, interpretation was based almost completely on serial changes, rather than on comparison to a table of normal values.

DISCUSSION

Even with stringent electrocardiographic criteria, it appears that 15 to 20 per cent of patients with measles show evidence of involvement of the heart. As in rheumatic fever and diphtheria, the electrocardiographic changes in measles are transient, and since some of our patients had an inadequate number of records during the course of their illness, it may be concluded that our estimate is conservative.

It may reasonably be questioned whether the demonstration of transient electrocardiographic abnormalities is adequate evidence for the diagnosis of myocarditis. In none of our cases was there clinical evidence of cardiac involvement. Nevertheless, these findings could not be attributed to fever. Since all but one of these patients were well hydrated and had a normal oral intake, it seems unlikely that acid-base balance disturbances played any important role. The abnormal tracings could, therefore, not be attributed to any known extracardiac factor.

In a previous study of diphtheria,[14] it was demonstrated that clinical evidence of myocarditis was present in only a small number of the cases showing abnormal tracings. Yet pathological study sometimes disclosed more widespread myocardial damage than would have been expected from the transient minimal electrocardiographic changes observed during life. No such pathological correlation was possible in the present study. Nevertheless, it is tempting to speculate that anatomical involvement of the heart does occur in measles, but is rarely, if ever, severe enough to be clinically detectable.

CONCLUSIONS

1. A study of 395 electrocardiograms in 106 patients with measles is reported.

2. Using stringent criteria, 19 per cent of the patients showed electrocardiographic abnormalities.

3. These findings could not be attributed to the occurrence of complications, fever, or to disturbances in acid-base balance.

4. Age, sex, and clinical severity of the disease seemed to play no important role in determining the incidence or character of electrocardiographic changes.

5. Abnormal tracings appeared as early as two or as late as twenty days after the onset of the rash, and usually reverted to normal within a week.

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OSSIFYING FIBROMAS (FIBROUS DYSPLASIA) OF THE FACIAL BONES IN CHILDREN AND ADOLESCENTS

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THE problems of diagnosis and, of even greater importance, the correct treatment are of particular interest in the handling of ossifying fibromas of the facial bones. The presence of a painless swelling in the face of a child, even though considered to be benign, presents the surgeon with the alternative of either removing the tumor as completely as possible through an external approach, or using an oral approach, which affords less visibility to the tumor mass. The principal reason that the oral approach is used is to avoid an external scar on the face, however slight. An attempt is made by this less extensive approach to restore normal contours with only minimal effort extended to effectively remove the bulk of the pathologic process.

In the past ten years, from 1944 to 1954, thirty-four patients with fibrous dysplasia were treated at Duke Hospital. Twenty of these patients were under 18 years of age with symptoms for as long as six years. The maxilla was involved in approximately 70 per cent of the patients. The mandible was found to be involved in 20 per cent and the ethmoidal and orbital regions in the remaining 10 per cent.

The youngest child in our series was 4 years of age. Twenty-four (70 per cent) of our patients were females.

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Different methods of treatment were used with varying degrees of success in the above-mentioned cases. Evaluation of these cases has resulted in a more uniform and effective clinical and surgical result.

ETIOLOGY AND DEVELOPMENT

It has been established that the embryonic connective tissue (mesenchyme) is the precursor of osteogenesis. In most of the bony skeleton, cartilage is formed first from the mesenchyme and this is gradually replaced by ossification which occurs slowly along the sides and interior of the cartilage (endochondral ossification). The facial bones, however, are formed mainly from mesenchymal cells which differentiate into fibroblasts which, in turn, form collagenous fibers and osteoblasts. These proceed to form the characteristic organic intercellular substance of bone (intramembranous ossification[1, 2]).

The formation and development of ossifying fibromas are considered by many[3-8] to be directly related to some embryologic dysfunction occurring during intramembranous ossification and which may be seen clinically years later in one or occasionally multiple areas in the facial bones.

It has been suggested more recently by others[9-13, 31, 33] that ossifying fibromas of the facial bones represent a variant of fibrous dysplasia of the bone

without change in blood calcium or phosphorus.[29]

Schlumberger,[13] in a recent report, suggested that the ossifying fibromas represented a modified bony repair process following injury. This has not been substantiated in other series.[3, 8, 14, 17, 28, 30, 32] It has been noticed in our own series, however, that only five of our cases refer the onset of their difficulties to some facial trauma or tooth infection.

GENERAL APPEARANCE

There may be considerable deformity due to this benign growth, including even proptosis and general displacement of the orbital contents (Fig. 1). There may also be marked enlargement of one side of the face, with or without impairment of vision (Figs. 2, *A* and *B*, and 5, *A*). In the mandible the growth process may be extensive and resemble an adamantinoma clinically. Fibrous dysplasia in the mandible was found to occur in the region of the angle of the mandible or in the anterior mandibular area.

Fig. 1.—Area of involvement included frontal and ethmoidal sinuses and wall of left orbit with two-year history. First noticed at age 16.

Painless swelling was the most uniform complaint and the most significant clinical finding.

HISTOPATHOLOGY

The microscopic appearance varies greatly, depending upon the individual ossifying fibroma (Fig. 3). Thoma[8] places them into one of three categories, depending on the amount of fibrous tissue, immature bone (osteoid), or the presence of a fibrous marrow with mature bone. Stones mentions "whorl-like formations of the spindle-shaped connective tissue cells and also the presence of multinucleated giant cells."[11, 19, 23] Geschickter[16] and others[15, 17] described the presence of these psammoma-like bodies of osteoid typical of ossifying tumors of the membranous bones.

Billing and Ringertz[20] divide fibro-osteomas into four different histological types, depending on the degree of maturity, the least differentiated type being rich in cellular connective tissue with many osteoid clumps, centrally calcified and peripherally poor in calcium. The other three groups become progressively acellular with a greater proportion of functionless bone in each succeeding category, and the most mature type is classified as an osteoma.[22] Occasionally the ossifying fibroma must be differentiated from the osteogenic sarcoma and this can be done by the absence of mitoses in the connective tissue cells and osteoblasts. Eden and others[3, 5, 6] reported a type of ossifying fibroma arising from the

Fig. 2.—*A* and *B*, A 16-year-old girl with four-year history of mass gradually increasing in size. Located in right maxilla. X-ray treatments without effect on growth or size of tumor. *C*, Shows large tumor mass filling entire right antrum with considerable expansion and distortion of adjacent bones. Notice homogeneous density. *D*, Two years postoperative with residual depression to be corrected, if necessary, at a later date with a fat fascial graft. Fergusson type incision inconspicuous.

periosteal region and forming a mushroomlike protuberant swelling with resultant loosening and displacing of the adjacent teeth.

RADIOLOGIC EVALUATION

The degree of calcification and the amount of osteoid substance present in the ossifying fibroma will influence the radiopacity and give considerable variance roentgenographically.

When there is maxillary involvement, particularly in the younger age groups, x-ray examination often reveals a homogeneous density with a stippled appearance, much like the peel of an orange (Fig. 2, *C*).[8, 24] This finding will disappear in the older age groups, as there is a tendency to greater density because of the increased ratio of bone to fibrous tissue.[26] The margin of tumor mass is generally blurred and irregular with areas of varying density often appearing in the same ossifying fibroma.[25]

Dentigerous cysts, fibromyomas, giant-cell tumors and adamantinomas have been diagnosed erroneously instead of an immature ossifying fibroma. A careful roentgen technique and evaluation will usually aid considerably in eliminating the odontogenic tumors. Dentigerous cysts rarely invade adjacent root apices, while the adamantinoma can be eliminated by examining the roentgenogram carefully for calcified tissue elements and multilocular rarified areas. The presence of calcified elements will also eliminate the possibility of a fibromyxoma (although a histologic examination may be necessary for final elimination). Giant-cell tumors usually exhibit a more pronounced cellular design or ragged, fine network.[21]

Fig. 3.—Relatively immature ossifying fibroma with predominance of cellular connective tissue and scattered areas of osteoid tissue.

In our series, the patients with maxillary involvement revealed considerably more radiopacity by roentgenogram than did those patients with mandibular involvement. Some of the mandibular tumors had areas of decreased density with cystlike characteristics (Fig. 4). The majority of the patients with maxillary involvement had a more diffuse growth pattern with the exception of three patients who had well-circumscribed lesions that were removed in toto.

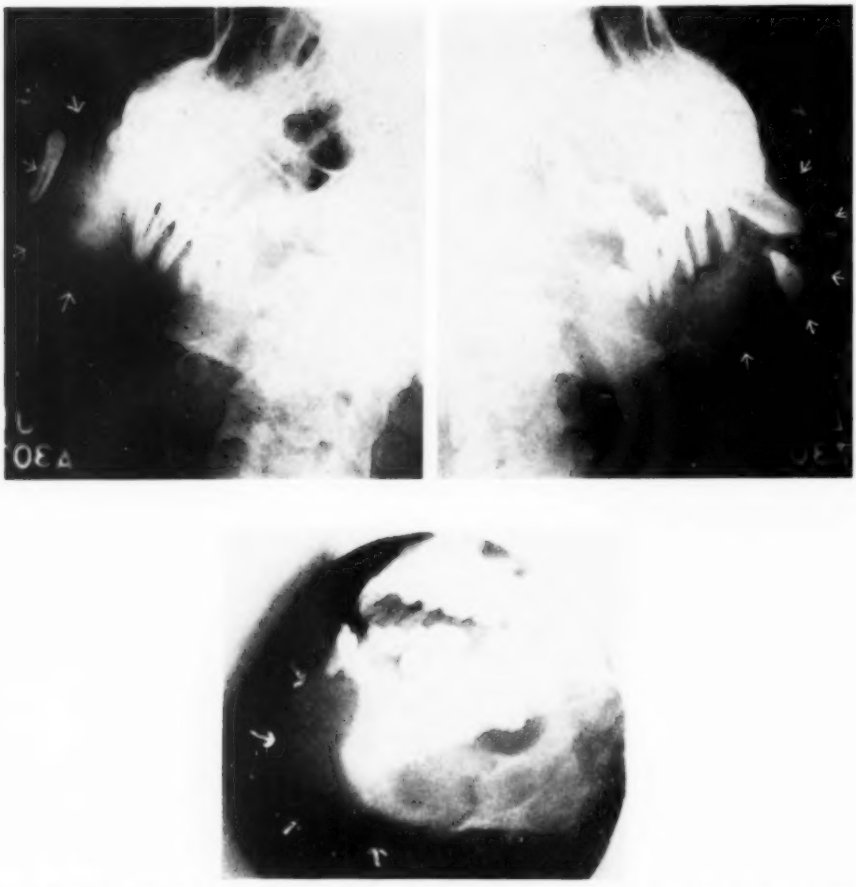

Fig. 4.—History of diffuse swelling of entire anterior mandible for three and one-half years prior to admission. X-rays revealed somewhat multiloculated appearance, new bone formation, and also bone resorption with impacted cuspid tooth. First noticed when 16 years of age.

COURSE AND TREATMENT

The duration of symptoms varied in our series from four months to six years, with the average being about two years. In the younger age groups, the tendency for recurrence was evident when the most conservative type of surgery was utilized. Three of the

Fig. 5.—*A*, A 5-year-old girl with history of swelling in right cheek for three months. *B*, A Fergusson type incision was made, taking advantage of the natural creases of face. *C*, Excellent exposure of tumor mass which is seen to involve almost the entire right maxillary area. D, Six months' postoperative result with inconspicuous scar.

patients returned for further surgery every few years because of increasing deformity. This consisted of reshaving and contouring the involved bone through an oral approach.

The procedure of choice as evolved during the past few years at Duke Hospital is one of conservatism when the presenting ossifying fibroma has a history of slow growth with minimal or no deformity.

When there is maxillary involvement and the benign process can be adequately recontoured through an oral approach, a modified Caldwell-Luc approach is utilized. If an oral approach is not feasible because of the size or location of the growth process, a modified Fergusson approach is easily performed, yielding an adequate exposure with minimal scarring postoperatively (Fig. 5). Another indication for using this type of approach would be if the mass was well circumscribed and an increase in the exposure would enable the operator to remove it completely.

The mandibular ossifying fibromas were all in the body, and a concealed submandibular incision was used. This gave excellent exposure with minimal noticeable postoperative scarring, even though there was extensive involvement of the mandible.

The use of x-ray and radium therapy has been reported.[3, 27, 28] This method was not used in the younger age groups because of possible injury to the growth pattern of the facial bones and teeth. Surgery was found to be the procedure of choice.

SUMMARY AND CONCLUSIONS

The origin of ossifying fibromas must be considered to be in doubt with two main groups of thought. One group favors the premise that these tumors arise only from membranous bone, as found in the face and skull. The second group believes that an ossifying fibroma is a variant of monostotic fibrous dysplasia.

The large rapidly-growing type of ossifying fibroma is the most difficult to treat, both from the esthetic and the surgical viewpoint.

Thirty-four cases of ossifying fibromas have been presented with twenty in the younger age group. These appeared to be benign bony processes which physically varied from a very soft, almost entirely fibrous mass, to a hard, more solid tumor.

Complete visualization and removal of extensive ossifying fibromas of the facial bones can be accomplished by means of an extraoral approach with minimal postoperative deformity.

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BLOOD AND CEREBROSPINAL FLUID LEVELS OF INTRAMUSCULAR OXYTETRACYCLINE

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THE reported levels of oxytetracycline in the cerebrospinal fluid of normal children usually ranges from 0 to 2 μg per cubic centimeter and does not alone seem related to the size of the dose, but also to duration of therapy preceding the analysis.[1] With increasing evidence of value of this drug in treatment of purulent meningitis, further study of blood and cerebrospinal fluid levels of oxytetracycline is needed. The purpose of the paper is to report on simultaneous serum and cerebrospinal fluid levels in a small group of five controls and of eight cases of purulent meningitis.

PROCEDURE

The oxytetracycline used in this study is the present form of the intramuscular preparation now marketed commercially as Terramycin.* This is furnished in 100 mg. vials, which before administration should be diluted to a concentration of 50 mg. per cubic centimeter with either sterile water or normal saline. The diluted material also contains 50 mg. per cubic centimeter of magnesium chloride and 2 per cent procaine hydrochloride. Potency is maintained for at least five days when stored in an ordinary refrigerator. It must be given deep intramuscularly and sites of injection constantly rotated. Technical assistance was furnished by the Pfizer Laboratories in the determination of the serum and the cerebrospinal fluid levels by the turbidimetric bio-assay described by Kersey.[2] Appropriate blanks and known controls were also submitted for check analysis. Patients used for serum and cerebrospinal levels were consecutive patients with meningitis admitted to the clinic service of the Los Angeles Childrens Hospital from January, 1954, to April, 1954. Control studies were done on routine surgical admissions without evidence of systemic disease or abnormality.

CONTROL OXYTETRACYCLINE SERUM LEVELS

The meningococcus, pneumococcus, and *Hemophilus influenzae*, type B, organisms are among the group of susceptible bacteria which are sensitive to oxytetracycline serum levels of 0.3 to 5.0 μg per cubic centimeter.[3] It is noted in Fig. 1 only one patient showed a level higher than 0.3 μg per cubic centimeter eight hours after a single dose of 6 mg. per kilogram of oxytetracycline given intramuscularly. Serum levels varied from zero to 1.2 μg per cubic centimeter. Three had zero levels nine hours after the original dose.

Fig. 2 shows that a single 12½ mg. per kilogram dose results in a higher and more uniform serum level. In all four controls serum levels of 1.2 to 2.5 μg per cubic centimeter were maintained throughout the eight hours.

From the Los Angeles Childrens Hospital, and Department of Pediatrics, School of Medicine, University of Southern California.

*Chas. Pfizer & Co., Inc.

Fig. 3 again reveals that a single dose of 18 mg. per kilogram maintains a consistent serum level of 2.5 μg per cubic centimeter for eight hours.

eight-hour levels range from 1.25 to 5 μg per cubic centimeter. In general, the eight-hour levels are not too dissimilar to those of Fig. 3.

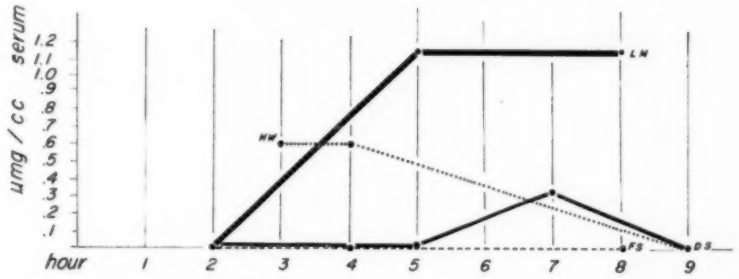

Fig. 1.—Oxytetracycline serum levels over an eight-hour period after a single intramuscular dose of 6 mg. per kilogram.

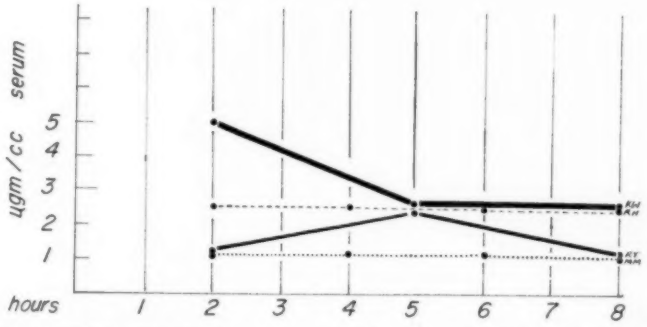

Fig. 2.—Oxytetracycline serum levels over an eight-hour period after a single intramuscular dose of 12½ mg. per kilogram.

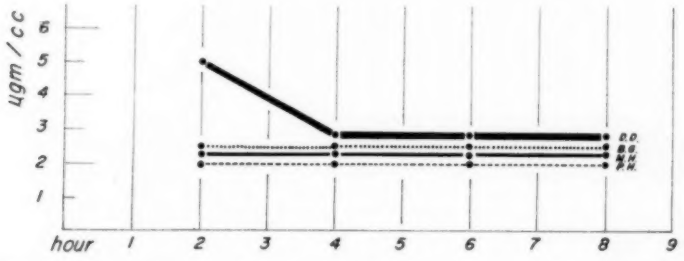

Fig. 3.—Oxytetracycline serum levels over an eight-hour period after a single intramuscular dose of 18 mg. per kilogram.

Fig. 4 shows that a dose of 25 mg. per kilogram produces higher levels ranging from 5 to 10 μg per cubic centimeter at the one-hour period. The

All of the twelve- and twenty-four-hour levels tested with the doses noted above did not reveal significant oxytetracycline levels. This is in contrast

to the results of O'Regan and Schwarzer.[4] One patient received a dose of 50 mg. per kilogram. The one-hour and two-hour levels were 40 and 20 μg per cubic centimeter; however, the six-hour level was only 5 μg per cubic centimeter. In general, it would seem that increased dosage results in higher initial peak in the serum level, but at the eight-hour level the end results are not too dissimilar from the results of the 18 mg. per kilogram dose.

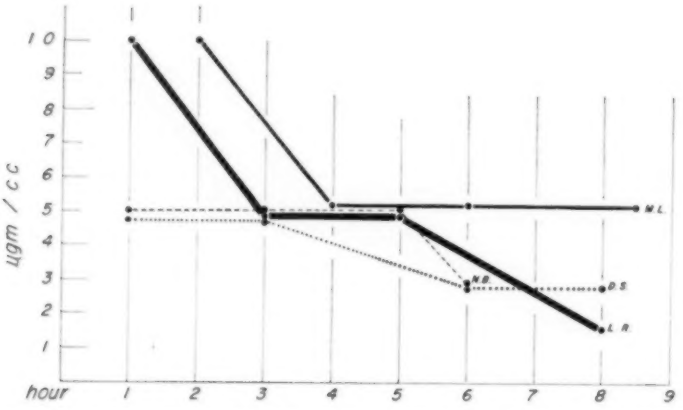

Fig. 4.—Oxytetracycline serum levels over an eight-hour period after a single intramuscular dose of 25 mg. per kilogram.

TABLE I. CONTROL SERUM AND CEREBROSPINAL FLUID OXYTETRACYCLINE LEVELS

PATIENT	DOSE MG./KG./DAY	HOURS ON MEDICATION	SERUM μG/C.C.	CEREBROSPINAL FLUID μG/C.C.
1. D. S.	100	24	10	0
		48	5	0
		72	5	2.5
2. R. G.	70	24	80	0
		48	40	1.25
3. J. C.	70	24	5	0
4. R. G.	60	24	–	0
5. G. J.	60	72	5	0

SERUM AND CEREBROSPINAL CONTROL LEVELS

Table I shows the results obtained from simultaneous serum and cerebrospinal fluid determinations obtained approximately twenty-four hours after initiation of therapy in five patients without inflammation of the central nervous system. Intramuscular oxytetracycline was given in equally divided doses at six-hour intervals. Six cerebrospinal fluid determinations revealed no detectable drug in spite of adequate serum level of 5 to 80 μg per cubic centimeter. Two patients had levels of 1.25 and 2.5 μg per cubic centimeter, respectively, but these two samples were obtained after they had been on therapy for two and three days, respectively.

SERUM AND CEREBROSPINAL FLUID LEVELS IN PURULENT MENINGITIS

Table II shows studies of eight patients with purulent meningitis treated

with oxytetracycline alone. These children were started on intravenous therapy and then switched to the intramuscular form because of the greater ease of administration. The levels obtained are substantially greater than those obtained in the normal controls. Again there appeared little correlation with serum levels. Occasionally spinal fluid levels while on intramuscular medication are noted to be higher than on intravenous administration. This is thought to represent accumulation in the spinal fluid as shown by Wood and Kipnis.[1]

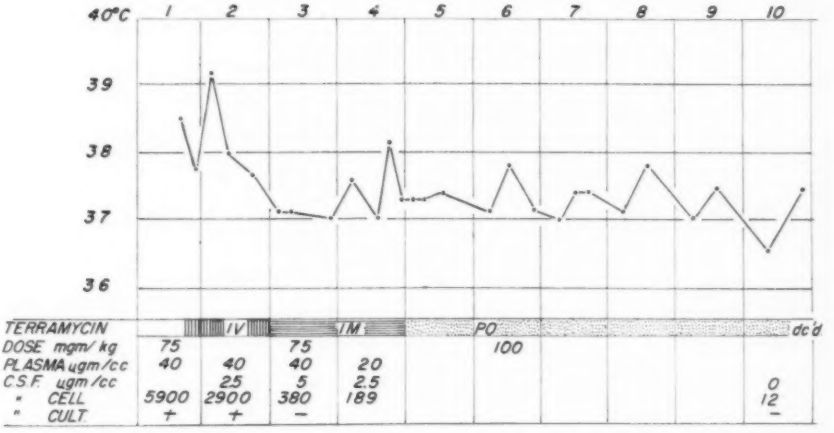

Fig. 5.—Clinical course of patient G. F. *Hemophilus influenzae*, type B, meningitis treated with Terramycin. 100 mg. per kilogram per day.

TABLE II. SERUM AND SPINAL FLUID DETERMINATIONS IN PURULENT MENINGITIS

PATIENT	DOSE MG./KG./DAY	HOURS ON MEDICATION	INTRAVENOUS SERUM	INTRAVENOUS CSF	INTRAMUSCULAR SERUM	INTRAMUSCULAR CSF
1. M. S.	100	24	10	5		
		48			10	5
		72			10	2.5
		120			–	5
2. R. W.	100	24	80	2.5		
		48	20	0.315		
		96			10	5
3. R. G.	100	24	5	–		
	50	72			20	2.5
4. G. F.	100	24	40	2.5		
		48	40	5		
		72			20	2.5
5. L. C.	85	24	20	1.25		
	55	48	20	1.25		
		96			10	1.25
6. D. S.	75	1	5	0		
		24	80	2.5		
		144			–	5
7. L. H.	100	24	10	2.5		
		48	10	2.5		
		72	10	2.5		
		96			10	2.5
8. G. J.	75	24	0	0		
		48			1.25	0.625

DISCUSSION

It would appear from these data that therapeutic plasma levels of 1.25 to 2.5 μg per cubic centimeter of oxytetracycline can easily be maintained for eight-hour periods using 12 to 18 mg. per kilogram doses.

The eight cases of purulent meningitis treated with oxytetracycline alone consisted of five cases of meningococcus, one of *H. influenzae*, type B, one case of pneumococcus, and one type undetermined. Seven of the eight patients responded promptly to therapy and recovered without neurological sequelae. Fig. 5 shows the clinical course of patient G. F. Patient L. H. had meningococcus meningitis which merits further comment and therefore is given in detail.

Patient L. H. was an 8-month-old Negro male infant who was admitted with a one-week history of respiratory infection with fever and anorexia. Physical examination revealed a bulging anterior fontanel, stiff neck, bilateral inflamed tympanic membranes, and rhonchi throughout the chest. The cerebrospinal fluid examination showed cloudy fluid with 1,100 cells per cubic millimeter, 85 per cent polymorphonuclears, and meningococcus was cultured. He was started on intravenous oxytetracycline, 75 mg. per kilogram per day, and sensitivity studies showed the organism to be very sensitive to oxytetracycline. Daily lumbar punctures were done, and although his clinical condition remained good, he remained febrile and the spinal fluid remained purulent. This was in spite of blood and spinal fluid levels of 10 and 2.5 μg per cubic centimeter, respectively, of oxytetracycline. After the fourth day of therapy the spinal fluid still contained 2,700 cells, so penicillin and sulfonamide therapy was substituted for oxytetracycline, with recovery. Spinal fluid cultures were negative throughout this period.

SUMMARY

1. Oxytetracycline given in 12 to 18 mg. per kilogram doses resulted in consistent serum levels of 1.5 to 2.5 μg per cubic centimeter over an eight-hour period when given intramuscularly.

2. Minimal amounts of oxytetracycline were detected in the spinal fluid of normal controls without central nervous system inflammation.

3. Patients with meningeal inflammation consistently showed levels between 1.25 and 5 μg per cubic centimeter of spinal fluid.

4. Eight patients with meningitis were treated with oxytetracycline alone. Seven recovered uneventfully. One patient failed to recover on this therapy, but was cured with substitution of penicillin and sulfonamides.

I am grateful to Dr. M. Carson for his help in writing this paper.

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THE SERUM CHOLESTEROL AND LIPOPROTEIN LEVELS IN MONGOLISM

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ALTHOUGH the mongoloid deficiency (congenital acromicria) is the most frequent of the congenital growth deficiencies, occurring three to four times in every 1,000 births, an understanding of the biochemistry of this disorder is still meager.[1] In spite of the fact that biochemical and biophysical investigations with radioactive iodide have rendered some relevant data,[2] no consistent changes have appeared which will characterize all cases. In 1953 Simon and associates[3] presented the results of an investigation on mongolism which led them to conclude that "the level of large molecule lipoproteins of the S_f12-20 class were definitely elevated when compared to the normal controls." Since the serum cholesterol level in mongolism is usually within the range seen in normal subjects, the observation that mongolism may be associated with the occurrence of abnormal serum lipoprotein patterns seems to offer a new clue which may facilitate the understanding of the biochemistry of mongolism. Gofman and others[4] had previously described a similar elevation of the lipoprotein molecules in arteriosclerotic patients. It was also of some interest to consider the mongoloid subjects in relation to the lipid disturbances associated with arteriosclerosis.[5]

The following study compares the serum cholesterol and lipoprotein levels of fifty-four mongoloids with those of fifty-four nonmongoloid but defective children living in the same institution, under the same nutritional conditions and the same arrangements of care and activity. The values were also compared with those of 1,039 normal subjects. The subjects were age- and sex-matched for these comparisons.

METHODS

The persons afflicted with mongolism used in this study lived as patients at the Walter E. Fernald State School, Waverley, Massachusetts. A definite diagnosis of mongolism was established in each subject after careful diagnostic study by experienced clinicians. The institutional control group consisted of subjects afflicted with cerebral palsies or prenatal developmental disorders of a variety of causes. Each of the control cases was matched according to chronological and mental age with a corresponding mongoloid patient.

The conditions of environment, including diet, were similar for all of these. The "normal" comparison group consisted of active, healthy subjects consuming a variety of diets and

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The laboratory measurements of this study, which were carried out in the Department of Nutrition, were supported in part by grants from the National Heart Institute (No. H-932), National Institutes of Health, Bethesda, Md., and by grants from the Albert and Mary Lasker Foundation, New York; the Kellogg Company, Battle Creek, Mich., and General Mills, Inc., Minneapolis, Minn.

living in a variety of environments who were studied in the course of other work. They were selected after a physical examination designed to identify the presence of acute or chronic diseases. The characterization of the three groups according to age, sex, and numbers is shown in Table I. For the present purposes, the groups were considered according to two major age groupings: under 25 years and equal or over 25 years.* Comparison made after further age subdivision does not influence the conclusions.

Table I. Age Distributions of the Subjects Studied

	MALE			FEMALE		
	AGE			AGE		
	<25 YR.	≥25 YR.	TOTAL	<25 YR.	≥25 YR.	TOTAL
Mongoloids	9	16	25	6	23	29
Institutional controls	9	20	29	7	18	25
Normal controls	13	765	778	35	226	261

The serum of freshly drawn blood was analyzed for total cholesterol by the method of Abell and co-workers.[6] The serum lipoprotein was measured by the ultracentrifuge technique of Gofman and associates.[4] These procedures were completed within seventy-two hours of the drawing of blood. The serum of each defective subject was supplied to the laboratory as a coded sample which did not permit the identity of the subject's clinical status. Single measurements were carried out and these results were then matched with the clinical data.

The statistical analysis of such lipid measurements is complicated by the non-normality of the distribution of groups of such measurements. We have found this characteristic to be typical of such serum lipid measurements.[7] This attribute taken with a large coefficient of variation $\left(\frac{\sigma}{\times}\right)$ which is also typical does not permit the application of conventional, small sample statistics for the evaluation of the meaning of observed differences. Two available alternatives are the transformation of measurements to some normally distributed function followed by conventional analysis or the construction of cumulative frequency curves relating the proportions of each comparison group to some arbitrary level of measurement followed by an evaluation of these proportion differences between groups using the chi square method. For the present comparisons we have used the latter procedure.

Another complication of comparison of the serum lipid levels of mongoloid subjects with either a group of non-mongoloid defectives or with normals is the abnormality of body build characteristic of mongoloids. Dwarfism and obesity are common. It has been shown by Gofman and Jones,[8] as well as by Walker,[9] the latter using the data of Dawber and associates[10] that there is a significant positive correlation between body weight and serum lipoprotein levels. It might be anticipated that for this reason alone the mongoloid subjects would show higher levels of serum lipids. However, the evaluation of body build in mongol-

*The normal control group includes subjects aged 25 through 49 years for males and aged 25 through 59 for females. These ages include the range of ages found in the mongoloid group.

TABLE II. A COMPARISON OF THE LEVELS OF SERUM CHOLESTEROL AND SEVERAL CLASSES OF LIPOPROTEINS OBSERVED IN MONGOLOID SUBJECTS WITH THOSE OF INSTITUTIONAL CONTROLS AND WITH NORMAL SUBJECTS

The percentage of subjects in the groups below an arbitrary level of concentration is shown. The significance of proportion differences was tested by the chi square method.*

		S_f12-20		S_f21-35		S_f35-100		TOTAL CHOLESTEROL		
	LEVEL	<20 MG. %	<30 MG. %	<20 MG. %	<30 MG. %	<40 MG. %	<60 MG. %	<175 MG. %	<200 MG. %	<250 MG. %
	N	PER CENT		PER CENT		PER CENT		PER CENT		
Males <25 years										
Mongoloids	9	11	89	89	100	44	89	67	89	100
Institutional controls	9	56	78	89	100	56	89	33	78	100
Normal controls	12	58	75	92	100	69	92		61	85
Females <25 years										
Mongoloids	6	33	50	83	83	67	83	33	83	100
Institutional controls	7	86	86	100	100	100	100	72	100	100
Normal controls	35	57	89	94	100	89	100		58	78
Males ≥25 years										
Mongoloids	16	19	69	88	100	81	100	44	63	94
Institutional controls	19	32	63	84	95	53	74	42	63	95
Normal controls	765	14	37	62	82	35	59		26	69
Females ≥25 years										
Mongoloids	23	4	35	65	87	74	91	13	26	78
Institutional controls	18	6	61	83	94	56	83	22	50	78
Normal controls	226	29	59	78	92	77	88		32	80

*Significant differences ($p \leq 0.05$) are bracketed.

oids is complicated by the lack of reference tables of height-weight relationships at these minimal heights.

For the present purposes standards of height-weight relations for these subjects of age 25 years or more were reached in the following manner: Regression equations relating the height to weight of adults were derived for each sex from the Metropolitan Life Insurance Company Tables of Ideal Weight.[11] Extrapolations for weights at heights below 60 inches were reached by substitution in these equations. For subjects between 18 and 25 years of age the same procedure was used except that one pound of weight was subtracted from the tabular "ideal weight" used for each year of age under 25 years.

For subjects under 18 years the tables of normal weight for given heights and ages of Stuart and Meredith[12] were used for extrapolation in a similar manner. The ratio of the observed weights to these derived "ideal weights" was then computed.

age showed a persistent tendency to higher lipoprotein and cholesterol levels. All the male mongoloids and the female mongoloids of 25 years or more showed irregular higher or lower levels of these lipids than did the institutional controls. Furthermore, the absolute levels of these serum lipids were not greatly different in the defective groups from those of the normal population. It is clear that these serum lipid measurements would not serve as means of discrimination between such groups; much less would they characterize individuals. There is little evidence from these measurements that mongolism is characterized by alterations of serum lipid patterns.

The comparison made in Table II indicated that the most persistent differences among the three groups compared were found with the female mongoloids under 25 years of age. More subjects of this group were found to have the classes of lipoproteins measured and the cholesterol at higher levels than did the comparison groups.

TABLE III. PER CENT OF SUBJECTS WITH RELATIVE WEIGHT OF 1.10 OR LESS*

AGE (YEARS)	MALE		FEMALE	
	INSTITUTIONAL CONTROLS	MONGOLOIDS	INSTITUTIONAL CONTROLS	MONGOLOIDS
<25	89	33	83	33
≥25	72	88	83	52

*Significant differences ($p \leq 0.05$) are bracketed.

RESULTS

The statistical summary and comparison of groups are shown in Table III. These data revealed but little evidence of serum lipid pattern characteristic of mongolism. When the mongoloid groups were compared with the institutional controls, only the female mongoloids of less than 25 years of

These findings may be related to a greater prevalence of fatness among this group. This hypothesis was examined according to the methods described for the two groups of defective subjects.

In Table III the weight data have been considered as cumulative frequency distributions and the compari-

son was made of the proportion of each group with relative weights* of 1.10 or less. The method indicated that with the exception of males 25 years of age and over, there were smaller proportions of mongoloids with relative weight of 1.1 and less than there were among institutional controls. The mongoloids tended to be fatter than the institutional controls.

This observation may account, in part, for the irregular tendency of the mongoloids to show higher serum lipid levels except the males of 25 years and more. It appears reasonable to conclude that the higher levels of lipids observed among the mongoloids may be attributed to this increased prevalence of fatness. Such progeria as exists among mongoloids must be attributed to other causes than a simple elevation of serum lipids. These measurements of serum lipids will be of little use in characterizing mongolism.

SUMMARY

A comparison of the serum total cholesterol levels and certain classes of serum beta-lipoprotein levels among fifty-four mongoloid subjects, fifty-four institutional controls, and 1,039 well subjects has failed to reveal consistent differences. Such evidence of higher serum lipid levels as was found among the mongoloids appears to be explained by a greater prevalence of obesity in those subjects. Mongolism is not characterized by unusual serum lipid patterns.

*Relative Weight $= \frac{\text{Observed Weight}}{\text{Ideal Weight.}}$

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THE BROCK OPERATION FOR PULMONARY STENOSIS

Review of Thirty-Nine Cases

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ONE of the greatest accomplishments of modern cardiac surgery has been the development of operative procedures for the relief of pulmonary stenosis. Two main groups of procedures have been devised. These are the establishment of extracardiac shunts, as in the Blalock[1] and Potts[2] operations, and a direct attack upon the stenotic pulmonary valve or infundibulum according to the method of Brock.[3] It is generally accepted that in the case of pulmonary stenosis with intact ventricular septum the Blalock procedure is contraindicated[4] and the valve must be dealt with directly by Brock's method. Brock[5] was the first to advocate that the pulmonary stenosis associated with the tetralogy of Fallot also could be relieved by his procedure. Experience has shown, however, that the type of operation indicated in the tetralogy of Fallot varies with the anatomic peculiarities of a given case. Precise preoperative anatomic diagnosis has, therefore, become of great practical importance rather than of merely academic interest. The surgeon would like to know preoperatively what type of stenosis is present: valvular, postvalvular, infundibular, or combined valvular and infundibular. If an infundibular stenosis is present, is the obstruction a thin fibrous diaphragm, or a long narrow muscular tract? Is a pulmonary artery present or completely atretic? How much overriding of the aorta is present? The responsibility of the medical team is to attempt to answer these questions whenever possible.

It has been shown that congenital cardiac malformations can be studied and treated in community general hospitals where adequate facilities and well-trained personnel are available.[6, 7] This paper is a report of thirty-nine patients with pulmonary stenosis who were treated at such a community general hospital by the Brock procedure. Our aim in this report is twofold: first, to contribute pertinent and interesting clinical information acquired during the course of this study, and, second, to evaluate critically the Brock procedure as applied to the tetralogy of Fallot.

MATERIAL

The first thirty-nine patients operated upon for the relief of pulmonary stenosis by the Brock procedure have been selected for review. A summary of the clinical findings in these patients will be found in Table I. There were twenty-four males and fifteen females. The ages ranged from 3 months to 36 years. The largest age group consisted of twenty-

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six patients between their sixth and twenty-second years. There were eleven patients under 6 years of age, and two patients were over 25 years of age.

Twenty-seven cases of pulmonary stenosis were associated with an interventricular septal defect and overriding of the aorta (tetralogy of Fallot). There were eleven cases of pulmonary stenosis with intact ventricular septum and coexistant interauricular communications of varying degree, and one case of pure pulmonary stenosis with intact septa. The diagnosis was established in the majority of patients on the basis of clinical findings and ordinary laboratory procedures. Angiocardiographic and catheterization studies were performed in certain cases where the diagnosis was not certain or for the collection of scientific data.

CLINICAL ASPECTS

All patients submitted to operation manifested symptoms. Symptoms appeared earlier in life and were more severe in the tetralogy of Fallot group. Dyspnea was the most consistent symptom. Orthopnea was noted in two cases and periodic loss of consciousness occurred in four cases. Overt cardiac failure was present in two cases. The degree of disability was graded according to criteria of functional capacity as set down by the New York Heart Association. Fourteen patients were classified in Group II, twenty-two patients in Group III, and three cases fell into Group IV.

Clinical cyanosis was present in all cases of the tetralogy of Fallot and in seven of the cases of pulmonary stenosis with intact ventricular septum. In the five cases of the latter category in which cyanosis was not evident clinically, arterial oxygen saturation determinations showed definite evidence of oxygen desaturation in one case, normal oxygen saturation (above 94 per cent) in two cases, and in the remaining two cases borderline figures were obtained. Clubbing of the digits was present in twenty-five cases.

A thrill was palpable in fourteen cases of the tetralogy of Fallot, seven cases of pulmonary stenosis with intact ventricular septum and atrial septal defect, and the one case of pulmonary stenosis with intact septa. A systolic murmur was present in all cases and a diastolic murmur also was heard in several instances. A continuous murmur occurred in one case in which there was an associated patent ductus arteriosus. The second sound over the pulmonic area was frequently diminished or absent. However, in some cases, it was normal or even apparently accentuated. Therefore, we have not found that the intensity of the second pulmonic sound is an important diagnostic criterion. The blood pressure was not abnormal in any case in this series.

ROENTGENOLOGIC FINDINGS

Although the fact that in the tetralogy of Fallot the heart most often is normal in size is an important diagnostic criterion, in our series the heart was definitely enlarged in four cases and questionably enlarged in several others. The enlargement was not due to obvious heart failure. In the tetralogy group the pulmonary artery segment was concave in twenty-two cases and convex in five cases. In the latter group combined valvular

TABLE I. SUMMARY

CASE NO.	NAME	AGE	SEX	CYANOSIS		CLUBBING	DISABILITY	ROENTGEN FINDINGS		
				DEGREE	AGE AT ONSET			ENLARGED HEART	PULMONARY ARTERY CONTOUR	PULMONARY VASCULAR MARKINGS
										Tetralogy
1	M. R.	18 yr.	F	4+	Birth	Yes	IV	No	Concave	Diminished
2	L. F.	3 yr.	M	1+	6 mo.	No	IV	No	Concave	Normal
3	R. B.	7 yr.	M	4+	Birth	Yes	IV	No	Concave	Diminished
4	A. S.	21 yr.	F	4+	Birth	Yes	III	No	Concave	Diminished
5	E. N.	6 yr.	M	3+	Birth	Yes	III	No	Concave	Normal
6	R. D.	5 yr.	M	Intermittent	?	Yes	II	No	Concave	Diminished
7	D. B.	17 yr.	M	1+	Birth	Yes	III	Yes	Convex	Diminished
9	W. B.	3 mo.	M	2+	Birth	No	II	Yes	Concave	Diminished
10	R. H.	15 yr.	M	3+	10 yr.	Yes	II	No	Convex	Normal
11	S. B.	36 yr.	M	3+	Birth	Yes	III	Yes	Convex	Normal
13	R. M.	8 yr.	M	3+	Birth	Yes	III	No	Concave	Diminished
14	J. W.	21 yr.	M	2+	Birth	Yes	III	No	Concave	Diminished
15	M. F.	14 yr.	F	3+	Birth	Yes	III	No	Concave	Normal
16	L. K.	12 yr.	F	2+	9 mo.	Yes	III	No	Concave	Diminished
17	H. L.	7 yr.	M	3+	6 mo.	Yes	III	No	Convex	Increased
19	E. R.	3 yr.	M	2+	Birth	No	II	No	Concave	Normal
20	M. Mc.	3 yr.	F	Intermittent	10 mo.	No	II	No	Concave	Diminished
21	D. H.	10 yr.	F	4+	Birth	Yes	III	No	Concave	Normal
25	D. G.	13 yr.	F	1+	Birth	Yes	III	No	Concave	Diminished
27	R. H.	5 yr.	M	3+	Birth	Yes	II	No	Concave	Diminished
28	P. B.	8 yr.	M	2+	1 yr.	Yes	II	No	Concave	Diminished
29	D. D'A.	15 yr.	F	4+	Birth	Yes	III	No	Concave	Normal
30	B. F.	5 mo.	F	4+	Birth	No	III	No	Concave	Diminished
31	C. D'A.	20 mo.	F	Intermittent	Birth	No	III	Yes	Concave	Diminished
32	M. G.	4 yr.	F	2+	1 yr.	No	III	No	Concave	Normal
33	G. A.	10 yr.	M	2+	3 yr.	Yes	II	No	Convex	Diminished
34	L. O'G.	4 yr.	F	2+	2 yr.	Yes	II	No	Concave	Diminished
										Pulmonary Stenosis With Intact Ventricular
12	R. S.	16 yr.	M	Absent		No	II	Yes	Marked convexity	Diminished
18	G. N.	5 yr.	M	Absent		No	II	Yes	Convex	Diminished
22	R. V.	13 yr.	M	Absent		No	III	Yes	Marked convexity	Normal
23	R. T.	11 yr.	M	1+	?	No	III	Yes	Concave	Diminished
24	J. H.	16 yr.	M	3+	Birth	Yes	III	Yes	Marked convexity	Diminished
26	M. Mu.	10 yr.	F	Intermittent	?	No	II	Yes	Marked convexity	Diminished
35	M. K.	20 yr.	F	2+	Birth	Yes	III	Yes	Convex	Diminished

OF FINDINGS

ELECTROCARDIOGRAM			CATHETERIZATION PRESSURES				
AURICULAR HYPERTROPHY	RIGHT AXIS	RIGHT VENTRICULAR HYPERTROPHY	PULMONARY ARTERY	RIGHT VENTRICLE	ANGIOCARDIOGRAPHY	TYPE OF STENOSIS AT OPERATION	RESULTS
of Fallot							
						Valvular	Died
No	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Infundibular	Unimproved
Yes	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Valvular	Good
?	Yes	Yes				Valvular	Good
Yes	Yes	Yes		78/0		Combined	Good
Yes	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Valvular	Died 6 mo. postop.
?	Yes	Yes			No simultaneous opacification of aorta and pulmonary artery	Combined	Good
No	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Valvular	Died
No	Yes	Yes				Combined	Good
Yes	Yes	Yes				Combined	Good
Yes	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Infundibular	Good
Yes	Yes	Yes		70/0	Simultaneous opacification of aorta and pulmonary artery	Valvular	Good
Yes	Yes	Yes	12/0	125/0	No simultaneous opacification of aorta and pulmonary artery	Infundibular	Good
No	Yes	Yes	16/0	>85/0		Infundibular	Good
Yes	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Combined	Unimproved
Yes	Yes	Yes				Infundibular	Died
Yes	Yes	Yes			Simultaneous opacification of aorta and pulmonary artery	Infundibular	Good
Yes	Yes	Yes	10/2	67/0	Simultaneous opacification of aorta and pulmonary artery	Infundibular	Fair
Yes	Yes	Yes	20/5	145/5		Infundibular	Died
Yes	Yes	Yes	20/5	88/0		Infundibular	Died
No	Yes	Yes	10/2	120/0		Combined	Good
No	Yes	Yes	7/0	130/0		Valvular	Good
Yes	Yes	No			Simultaneous opacification of aorta and pulmonary artery	Combined	Fair
Yes	Yes	Yes		70/0	Simultaneous opacification of aorta and pulmonary artery	Combined	Died
Yes	Yes	Yes	20/8	135/5		Infundibular	Died
Yes	Yes	Yes	17/0	200/0		Infundibular	Good
Yes	Yes	Yes		100/0		Infundibular	Good
Septum and Interatrial Septal Communication							
No	Yes	No			Pulmonary stenosis Dilated pulmonary artery	Valvular	Fair
No	Yes	Yes	15/0-5	75/0	Dilated pulmonary artery	Valvular	Died
Yes	Yes	Yes		140/5-10		Valvular	Good
Yes	Yes	Yes		>33/0		Valvular	Good
Yes	Yes	Yes	15/7	190/5		Valvular	Good
Yes	Yes	Yes	18/8	67/0	Pulmonary stenosis Dilated pulmonary artery	Valvular	Good
Yes	Yes	Yes		170/0	Pulmonary stenosis Dilated pulmonary artery	Valvular	Died

TABLE

CASE NO.	NAME	AGE	SEX	CYANOSIS		CLUBBING	DISABILITY	ROENTGEN FINDINGS		
				DEGREE	AGE AT ONSET			ENLARGED HEART	PULMONARY ARTERY CONTOUR	PULMONARY VASCULAR MARKINGS
36	G. S.	10 yr.	M	3+	Birth	Yes	III	Yes	Concave	Diminished
37	M. T.	15 yr.	F	Absent		No	II	Yes	Concave	Normal
38	R. W.	11 yr.	M	2+	6 yr.	Yes	III	Yes	Marked convexity	Diminished
39	T. O'D.	7 yr.	M	2+	5 yr.	Yes	III	Yes	Convex	Diminished
										Pulmonary Stenosis
8	T. K.	25 yr.	M	Absent		No	II	Yes	Marked convexity	Diminished

and infundibular stenosis were present in four and infundibular stenosis alone in one. In the tetralogy group the vascularity of the lung fields was interpreted as diminished in seventeen cases, normal in nine, and increased in one case in which there was a coexistent patent ductus arteriosus. The estimation of the degree of vascularity of the lungs from x-ray films of the chest is admittedly difficult and often simply a matter of opinion. In the older age group, especially, pulmonary vascularity may appear normal or actually increased due to the establishment of extensive collateral circulation. All twelve cases of pulmonary stenosis and intact ventricular septum showed definite cardiac enlargement. In this group the pulmonary artery was convex in nine cases, and markedly dilated in six of these. In three cases the pulmonary artery segment was concave. Vascularity of the lung fields in these patients was diminished in ten cases and normal in two.

There were four cases of right-sided aortic arch. These all were in the tetralogy group, an important diagnostic point.

ELECTROCARDIOGRAPHIC FINDINGS

Complete electrocardiographic studies were carried out in thirty-eight cases, twenty-six of the tetralogy of Fallot and twelve of the pulmonary stenosis with intact ventricular septum. The predominant rhythm was a normal sinus mechanism, with a tendency toward sinus tachycardia. A significant degree of sinus arrhythmia was encountered only three times. Ventricular extrasystoles occurred in only one case and no other ectopic rhythm was encountered. The rarity of arrhythmias in cases of this type is striking, particularly in view of the fact that the heart disease is severe. Moreover, the right auricular pressure was elevated in fourteen of twenty-four patients submitted to cardiac catheterization. Increased intra-auricular pressure in this group of cases, therefore, did not predispose to the development of arrhythmias.

Disturbance of conduction also was rare. A-V conduction was abnormal in only one case; this patient with a tetralogy of Fallot had complete A-V heart block. None of the

TABLE I—CONT'D

ELECTROCARDIOGRAM			CATHETERIZATION PRESSURES				
AURICULAR HYPERTROPHY	RIGHT AXIS	RIGHT VENTRICULAR HYPERTROPHY	PULMONARY ARTERY	RIGHT VENTRICLE	ANGIOCARDIOGRAPHY	TYPE OF STENOSIS AT OPERATION	RESULTS
No	Yes	Yes	15/3	100/0		Infundibular	Good
Yes	Yes	Yes	17/4	130/0		Combined	Fair
Yes	Yes	Yes	15/5	155/0		Valvular	Good
Yes	Yes	Yes	18/3	90/0		Valvular	Good
With Intact Septa							
Yes	Yes	Yes			Pulmonary stensois Dilated pulmonary artery	Valvular	Good

cases of the tetralogy of Fallot showed intraventricular conduction defects, despite the fact that in most the right ventricular pressure was high. Three of the cases of pulmonary stenosis with intact ventricular septum exhibited right bundle branch block. In two of these an auricular septal defect was present, while in the third an intracardiac shunt was not demonstrated. These findings suggest that the appearance of right bundle branch block does not depend primarily upon right ventricular pressure but that it is more probably related to a developmental defect in the junctional tissues. This fact would account for the frequent association of right bundle branch block with auricular septal defects.

In all thirty-eight cases the mean electrical axis of QRS was deviated to the right. In thirty-six cases there was definite evidence of right ventricular hypertrophy, while in the other two cases the ventricular patterns were normal. Whenever the electrocardiographic findings revealed right ventricular hypertrophy there was a definite increase in right ventricular pressure on catheterization. Definite evidence of right auricular hypertrophy was seen in twenty-seven cases. It is of interest that the mean electrical axis of auricular depolarization was normal in all cases despite marked rotation of the mean electrical axis of QRS to the right in most. This finding suggests either that the average direction of depolarization of the auricles tends to be more nearly parallel with the anatomic axis of the ventricles than does the QRS axis, or, more likely, that the QRS pattern of right ventricular hypertrophy in the precordial leads is not entirely due to rotation of the heart.

CARDIAC CATHETERIZATION

Preoperative catheterization studies were carried out in twenty-three cases. Thirteen of these were in the Fallot group and the remaining ten were cases of pulmonary stenosis with intact ventricular septum. We were able to detect the presence of infundibular stenosis in only two cases out of eleven that proved to have infundibular stenosis at the time of surgery. Therefore, in our hands detection of infundibular stenosis by means of cardiac catheterization has not been

satisfactory. The catheter could not be passed into the pulmonary artery in six patients. In two patients uncontrollable arrhythmias developed which necessitated termination of the procedure before completion. The fact that the catheter does not enter the pulmonary artery does not necessarily indicate that the artery is small or absent. We have been unable to estimate the size of the pulmonary artery by catheterization. In a few instances the presence of marked stenosis was inferred from the observation that the oxygen content of blood withdrawn from the pulmonary artery while the catheter was occluding the stenosed pulmonic orifice had been remarkably reduced.

In general, the right ventricular pressure in the tetralogy of Fallot closely mirrored the femoral artery pressure, while in the intact ventricular septum group the right ventricular pressure usually exceeded the systemic pressure. In only about one-half the cases were we able to determine the site of intracardiac shunt by either oxygen saturation studies or by direct passage of the catheter through a defect.

We have found that right auricular pressures in pulmonic stenosis with intact ventricular septum have been slightly higher than in the tetralogy of Fallot. There was no obvious relationship between the height of the auricular pressure and the right ventricular end diastolic pressure which would indicate that cardiac failure was not responsible for the increased right auricular pressure. It is conceivable that a slight degree of relative tricuspid insufficiency might occur more readily in the pulmonary stenosis with intact ventricular septum group, in which right ventricular hypertension is greater.

An interesting observation was that the pulmonary artery pressure distal to the area of stenosis was consistently between approximately 12 and 20 mm. Hg, regardless of the height of the right ventricular pressure. As a corollary to this, it may be stated that the greater the degree of stenosis, the greater the fall of pressure across the stenosed area.

ANGIOCARDIOGRAPHY

Eighteen patients were subjected to angiocardiographic study. Thirteen were in the tetralogy of Fallot group and five were in the pulmonary stenosis with intact ventricular septum group. It should be emphasized that this procedure is not without danger, especially in severely cyanotic patients.

In the tetralogy of Fallot group simultaneous opacification of the aorta and pulmonary artery, which is characteristic of a high septal defect and overriding of the aorta, was demonstrated in eleven cases. The two cases in which simultaneous opacification did not occur probably represented examples of insignificant overriding of the aorta. We have been unable to estimate accurately the degree of overriding of the aorta. The five cases of pulmonary stenosis with intact ventricular septum and atrial septal defects did not exhibit simultaneous opacification of the aorta and pulmonary artery. The degree of right-to-left shunt through the atrial septal defect, therefore, could not have been of great magnitude.

The size of the pulmonary artery can sometimes be estimated by angiocardiography. In almost all cases of

the Fallot group the opacified pulmonary artery was smaller than the systemic aorta. In all five cases of the intact ventricular septum group the pulmonary artery was dilated and at times of larger caliber than the aorta.

It was hoped that angiocardiographic study in the tetralogy of Fallot would demonstrate the presence of infundibular stenosis. Here also we have been disappointed, because we have not been able to determine the presence of infundibular stenosis with a sufficient degree of accuracy by means of this procedure.

It may be stated that angiocardiography in this field is of value in that it might help to rule out other conditions which can closely simulate the tetralogy, such as single ventricle, transposition of the great vessels, common truncus arteriosus, and so forth; it might give some information as to the size of the pulmonary artery, and also show whether a pulmonary artery is present or completely atretic. However, angiocardiography has not enabled us to determine the presence or absence of infundibular stenosis, or the degree of overriding of the aorta. These two factors are the most important ones in the preoperative evaluation of any given case. Therefore, in general, angiocardiography in this category of congenital heart disease adds little information of importance which is not obtainable by clinical methods and less dangerous laboratory procedures, including catheterization.

RESULTS

The thirty-nine patients in this series underwent surgery for the relief of pulmonary stenosis by means of the Brock procedure. There were twenty-seven cases of the tetralogy of Fallot. Of these, the stenosis was valvular in six, infundibular in twelve, combined valvular and infundibular in eight, and in the last case there was postvalvular stenosis of the pulmonary artery. In the pulmonary stenosis with intact ventricular septum group twelve patients were operated upon. Of these, ten had pure valvular stenosis, one pure infundibular stenosis, and there was one example of combined valvular and infundibular stenosis.

In the cases of pure valvular stenosis, valvulotomy was done with the use of the valvulotome. Infundibular stenosis was corrected by resection of the stenotic area by use of a modified pituitary rongeur.[7] When valvular stenosis was combined with infundibular stenosis both lesions were dealt with at the same operation. In the one case of postvalvular stenosis, dilatation was carried out by means of sounds.

Up to the time of this writing there has been a total of ten deaths in our series. Nine were operative deaths; the one patient not considered an operative death did well for six months postoperatively and then died of a brain abscess. Of the nine operative deaths, seven patients were less than 6 years of age. Five of these patients were in the tetralogy of Fallot group. The stenosis was infundibular in three, valvular in one, and combined infundibular and valvular in the last. There were two deaths in the pulmonary stenosis with intact ventricular septum and auricular septal defect group. In two cases of the tetralogy of Fallot there was overriding of the aorta of more than 50

per cent. The cause of death was attributed to cerebral anoxia in five cases. In two cases it was believed that the pulmonary valve had been opened too widely. One patient died in acute pulmonary edema: in this case there was overriding of the aorta of more than 50 per cent. One patient with pulmonary stenosis with intact ventricular septum died on the operating table of ventricular fibrillation.

The over-all operative mortality rate for the entire group was 23 per cent, a rather high figure. However, it is to be emphasized that in the group of twenty-eight patients over the age of 5 years there were only two deaths, a mortality rate of 7.1 per cent.

The surgical results were classified as good, fair, and unimproved on the basis of clinical evaluation alone. Postoperative physiologic studies have not been completed in this series at this time. The result was considered good when the functional capacity was markedly improved and cyanosis was diminished or clinically absent. The result was considered fair when there was some improvement in functional capacity and the relief of cyanosis, although definite, was not so striking as in the group classified good. When no obvious benefit was derived from the operation the patient was classified as unimproved.

Of the twenty-nine patients who survived the operation, twenty-three obtained good results. In four patients the results were classified fair, and two patients were unimproved.

DISCUSSION

A correct preoperative diagnosis was made in every case in this series. No patient was referred for surgery who did not have pulmonary stenosis. Most often the diagnosis was arrived at clinically. In a few cases catheterization and angiocardiographic studies helped to establish the diagnosis. Although the major diagnosis was correct, precise information concerning the presence of valvular or infundibular stenosis, or the degree of overriding of the aorta could not be supplied to the surgeon.

In this series we were committed to performing the Brock operation, and our first case (March, 1950) was one of the earliest done in this country. The Brock procedure is universally accepted as the treatment of choice for pulmonary stenosis with intact ventricular septum. In this condition the Blalock procedure is actually contraindicated. If an extracardiac shunt is established, due to the increased volume of blood returning to the left auricle, the pressure in this chamber may rise and exceed that in the right auricle. The right-to-left shunt through an atrial septal communication acts as a safety valve for relief of excessive right auricular pressure and, therefore, if the shunt is reversed, right heart failure may quickly supervene.

In the treatment of the tetralogy of Fallot, on the other hand, the surgeon has a choice of procedures: either the Brock or Blalock operation. The Brock procedure has certain advantages. It gives the surgeon the opportunity to conduct a methodical exploration of the heart's exterior and interior anatomy. Probing for an interventricular septal defect, sounding for stenosis of the valve or infundibulum and recording of manometric pressure readings give infor-

mation which is not available during the performance of a shunt procedure. The Brock operation cuts down on the degree of venoarterial shunt and does not create an additional anomaly. The Brock procedure is less time-consuming than the Blalock, and, if the patient does badly, or develops ventricular fibrillation, the operation can be carried to completion rapidly. However, we have encountered certain difficulties with this procedure which merit discussion.

An important consideration is the determination of how widely the valve (or stenotic infundibulum) should be opened. If the valve is opened too widely, the following disturbances in physiology theoretically may occur. In the presence of a large ventricular septal defect a double outlet ventricle exists, as hypothesized by Selzer.[8] In order for life to be maintained in the presence of a double outlet ventricle, either pulmonary hypertension must develop or stenosis of the valve or infundibulum must be present. In the tetralogy of Fallot, it is the pulmonary stenosis which prevents the major portion of the left ventricular outflow from shunting into the low pressure pulmonary vascular system. When the valve is opened by the Brock procedure this protective mechanism is abolished abruptly. The requirements, therefore, of a successful operation under these circumstances are that the surgeon open the pulmonary valve to an optimal degree and not too widely. If the valve is opened to a correct degree an adequate pulmonary blood flow might result without excessive shunting of blood to the lung. The situation then would approximate the dynamics which obtain in the presence of a small ventricular septal defect.

In two cases early postoperative death was believed to be due to the fact that the pulmonary valve had been opened too widely, and the same technical error probably was made in one case unimproved by operation.

The following symptom complex results when the valve is opened too widely. Cyanosis disappears almost immediately and the patient becomes pinkish in color, giving one the false impression that a successful result has been obtained. The patient leaves the operating table in apparently good condition. However, he reacts poorly from the anesthesia or he may die without regaining consciousness. In the latter event, death is usually attributed to cerebral anoxia, whereas it may actually be due to an excessive arteriovenous shunt. When the patient reacts from anesthesia he is cold, clammy and apathetic, and apparently in shock. The blood pressure is low, the respirations are shallow and very rapid (as high as 80 per minute), and the pulse is fast, although the heart sounds are good. The color remains good. The liver enlarges rapidly but peripheral edema is not seen. At first the lung fields are clear to physical examination but later pulmonary congestion becomes manifest. The patient then becomes more dyspneic, râles are heard, and x-ray films of the chest reveal increased pulmonary vascular markings. It is believed that this symptom complex can be explained on the basis of an excessive left-to-right shunt following the removal of the compensatory factor of pulmonary stenosis in the presence of a large high ventricular septal defect. Some

of the symptoms may reflect a secondary deficiency of the systemic circulation due to the tremendous left-to-right shunt. It is interesting that pulmonary edema does not follow immediately upon creation of this shunt. This is due to the fact that the lung can accommodate a great increase in volume of circulation provided that the flow of blood out of the lung is not impeded.[9] At first this is so, since the left ventricle is adequate. Subsequently, however, the left ventricle fails under the burden of maintaining a tremendously increased output. When this occurs the outflow of blood from the lungs is obstructed and pulmonary edema results.

One of the difficulties with the Brock procedure, therefore, is that the surgeon must be able to determine just how widely to open the valve. This requires judgment which can be obtained only by experience, since no hard and fast rules can be made. It may be said that the opening should be widened gradually until a good flow of blood can be felt through the pulmonary artery, but the valve should not be opened to the maximum diameter of the artery. If the patient's color becomes pinkish immediately after the valve is cut, the chances are that the opening is too wide, and it may be anticipated that he will not do well. It is preferable that the patient be still somewhat cyanotic at the completion of the operation. In these cases, where the valve has been opened to an optimal extent, the cyanosis decreases gradually over a period of several weeks, coincident with a fall in the red blood cell count and hematocrit.

Another major disadvantage of the Brock procedure is that it is performed blindly within the heart. If the obstruction is due to a thin, fibrous septum, its removal is relatively simple and excellent results are obtained. On the other hand, if the infundibular stenosis is due to a long, narrow, muscular tract, the operation is difficult and sometimes actually impossible. Autopsy specimens of several of our unsuccessful cases showed an extensive narrowing of the infundibular tract which obviously could not have been corrected by a blind intracardiac procedure.

Unfortunately, our present methods of investigation do not furnish precise information concerning the abnormal internal architecture of the heart, so that one is forced to rely upon inference based on accumulated experience in deciding upon the type of procedure to be adopted in any given case. It is interesting that the majority of our operative deaths occurred in patients below the age of 6 years. Those children who are operated on early in life as an urgent necessity are the ones who have a severe lesion. The majority have an infundibular stenosis, frequently of the type with a long, narrow outflow chamber. In this connection it may be pointed out that clinical analysis of cases of the tetralogy of Fallot show a disproportionately high number of cases with valvular stenosis, whereas reports of autopsy series show a greater number of cases of infundibular stenosis.[10] Thus, in general, those patients with infundibular stenosis have a more serious lesion, are sicker, and are more likely to die in early life. Since infundibular stenosis is more common in the younger age group, below 6 years, and since by our present methods of

clinical investigation we cannot definitely establish the presence of valvular or infundibular stenosis, or the type of infundibular obstruction, we believe that in these patients a pulmonary systemic shunt procedure is preferable. In the future it is expected that an extracorporeal mechanical pump will be perfected which will permit an open intracardiac operation. Development of the technique of hypothermia may accomplish the same purpose. Therefore, the shunt procedure may be regarded as a temporary expedient to prolong the life of a patient until such time that an open operation can be done.

In the older age group, 6 years and above, however, where there is more likelihood that the stenosis is valvular and that an infundibular stenosis, if present, is not a severe one, the Brock procedure may be considered the first choice. Our mortality in this group was low, and the results were at least as good as those to be expected from a shunt procedure.

When overriding of the aorta is marked, 50 per cent or more, neither the Blalock nor Brock procedure is feasible. If a pulmonary systemic shunt is created, a marked increase in return flow to the left auricle and ventricle results; in the presence of marked overriding of the aorta, the left ventricle cannot expel this greatly increased volume of blood and failure will result. The same mechanism may be expected to occur if the stenotic pulmonary valve or infundibulum is opened by the Brock procedure. Therefore, for patients in this category, surgical treatment at present is contraindicated. Improved methods of diagnosis are to be hoped for so that the degree of overriding of the aorta can be estimated before subjecting a patient to operation.

SUMMARY AND CONCLUSIONS

1. Thirty-nine patients with pulmonary stenosis operated upon by the method of Brock are reviewed.

2. Pertinent clinical data are presented and discussed.

3. The correct preoperative diagnosis of pulmonary stenosis with or without a defect of the ventricular septum was made in all cases, usually on clinical grounds alone, without resort to special studies.

4. In the presence of the tetralogy of Fallot a precise delineation of the abnormal internal architecture of the heart could not be made.

5. The Brock procedure is the only one available for surgical relief of pulmonary stenosis without a ventricular septal defect.

6. In the treatment of the tetralogy of Fallot the surgeon has a choice of either the Brock or Blalock procedure.

7. The choice of operation is influenced by the following factors: the presence of valvular or infundibular stenosis, whether the infundibular stenosis is due to a fibrous septum or a long, narrow, muscular tract, the presence or absence of a pulmonary artery, the size of the pulmonary artery, and the degree of overriding of the aorta. Unfortunately, these questions cannot be answered with sufficient accuracy with our present methods of investigation, and, therefore, to a great extent the choice of operation is empirical.

8. The mortality of the Brock procedure is high in the tetralogy of Fallot in children below the age of 6

years. Since in this group a severe form of infundibular stenosis is likely to be present, the Blalock procedure should be done.

9. In the older age group of the tetralogy of Fallot, there is more likelihood that the stenosis will be valvular or that an infundibular stenosis will be less severe. In this group the mortality rate of the Brock procedure is low and the results are excellent. In this group, therefore, the Brock procedure is the one of choice.

10. In the presence of overriding of the aorta of more than 50 per cent, neither procedure is feasible and surgery is contraindicated at the present time.

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GASTROINTESTINAL DISTENTION IN INFANTS

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THE puzzling behavior of gastrointestinal gas has intrigued numerous investigators. Clinicians and laboratory workers have contributed equally to the voluminous literature on the problem of gaseous distention, but many questions remain to be answered. These problems are primarily of interest to the surgeon who must deal with paralytic and mechanical ileus in his everyday practice, but there are additional facets of the problem which are interesting to the pediatrician.

The three sources of gastrointestinal gas are: (a) food decomposition, (b) swallowed air, and (c) diffusion from the blood stream (Table I).

FOOD DECOMPOSITION

The gaseous product of food decomposition is chiefly CO_2, especially in the infant whose food consists largely of carbohydrates. Because of the rapid emptying time of the infant stomach, this gas is formed mainly in the small intestine by the action of fermentative bacteria. As protein and roughage are added to the diet, other gases are formed as shown on Table I. It should be noted that cellulose breaks down in the large bowel due only to bacterial action, since the enzyme cellulase is not present in human beings.[1] Putrifactive bacteria acting on proteins form odoriferous gases. Milk is the primary source of protein in newborn infants. By far, the largest amount of gas produced by food is CO_2 which is readily absorbed by the intestinal tract. Nitrogen is not a product of food decomposition.

SWALLOWED AIR

Animal experiments and clinical observations indicate that swallowed air may be considered the chief source of intestinal gas.[2-7] Wangensteen,[4] who with his co-workers has studied the problem extensively, states that 68 per cent of gastrointestinal gas is due to swallowed air. This concept does not fit the observed clinical facts according to Begg,[8] who claims that diffusion of gases from the blood stream is of more importance in distention.

Abdominal films of infants normally reveal gas in the small bowel, but this finding in adults is usually abnormal. The explanation of this difference is obscure. In general, pediatricians feel that infants readily swallow air, and they admonish parents to "take the bottle away as soon as it is emptied of milk lest the baby suck in air." Bottle nipples, used as pacifiers, are stuffed with cotton for the same reason. Moreover, many pediatricians feel that aerophagia is an important contributory cause of colic in infants.[9-12] The explanation is that the hungry or underfed infant starts crying and sucks on anything available. Both of these acts allegedly initiate aerophagia and intestinal distention.

The resultant colic causes more crying and establishes a vicious cycle.

It has also been contended that infants ingest air with each inspiration irrespective of the crying factor. Leigh and Belton[13] passed a tube into the infant's stomach and placed the free end under water. They found gas bubbling up through the water with each expiration, and they postulated air ingestion on inspiration due to a negative intragastric pressure.

TABLE I

GAS	CHIEF SOURCES	REMARKS
N_2	(a) Swallowed air ($N_2 = 79.02$ vol. %) (b) Diffusion from blood	Inert gas—never the end product of food decomposition
CO_2	(a) Diffusion from blood (b) Action of acid gastric contents on carbohydrates present in alkaline pancreatic and intestinal secretions (c) Action of fermentative bacteria on carbohydrates (d) Decomposition of cellulose	(c) In small intestine—bacillus bifidus, etc. (d) In large bowel: cellulose → CO_2 + fatty acids
O_2	(a) Swallowed air ($O_2 = 20.94$ vol. %) (b) Diffusion from blood	
H_2 CH_4 (marsh gas)	From cellulose	Formed only in large bowel by bacterial action since the enzyme cellulase is not present in man
H_2S NH_3 Indole Skatole	Action of putrefactive bacteria on proteins	Odoriferous gases; last three are found only in traces

TABLE II

CASE NO.	AGE	X-RAY EVIDENCE OF STOMACH GAS: FILM 1 FASTING	FILM 2 AFTER SUCKING ON EMPTY BOTTLE	FILM 3 AFTER DEGLUTITION	AMOUNT INGESTED (C.C.)	REMARKS
1.	12 da.	Moderate	No change	Marked increase	30	
2.	18 da.	Moderate	No change	Marked increase	60	
3.	18 da.	Moderate	Minimal change	No change	30	Infant burped before third film was taken
4.	18 da.	Minimal	No change	Marked increase	45	Fig. 1
5.	21 da.	Moderate	No change	Marked increase	30	Fig. 2
6.	1 mo.	Minimal	No change	Moderate increase	15	Note air ingested with only 15 c.c. of milk. Fig. 3
7.	3 mo.	Moderate	No change	Marked increase	45	
8.	3 mo.	Minimal	No change	Marked increase	45	
9.	4 mo.	Moderate	No change	Marked increase	30	
10.	5 mo.	Moderate	No change	Slight increase	30	Infant burped before third film was taken
11.	9 mo.	Moderate	No change	Moderate increase	240	Infant burped before third film was taken
12.	18 mo.	Moderate	No change	Moderate increase	30	Milk ingested in two minutes
13.	6 yr.	Minimal	No change	Marked increase	120	Fluid gulped down in eight seconds. Fig. 4

Soveri[14] found that infants do not swallow air by sucking on an empty bottle or their fingers. He concluded from his clinical experiments and x-ray studies that infants only swallow air during the act of deglutition. These observations obviously are in conflict with the beliefs of a good many pediatricians.

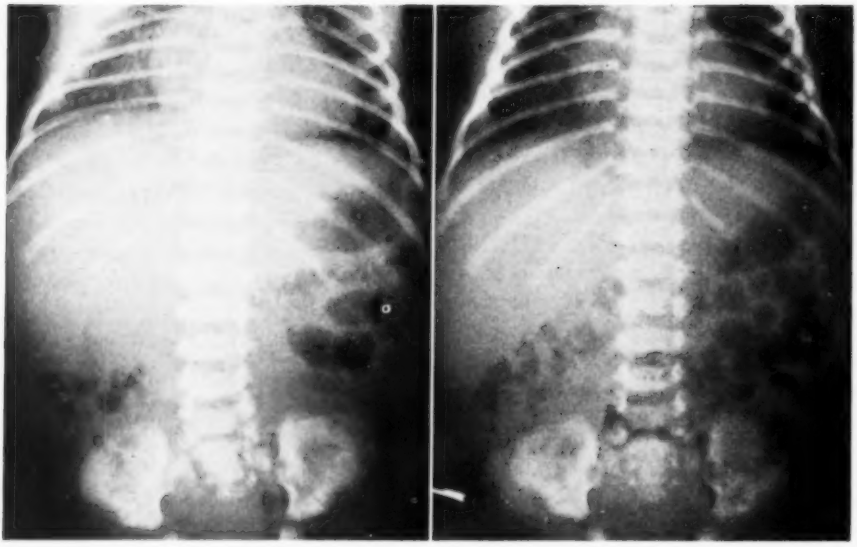
To evaluate Soveri's work, roentgenological studies were carried out on patients from the newborn nursery and the pediatric ward. Thirteen subjects were chosen ranging in age from 12 days to 6 years. A preliminary scout film of the abdomen was taken following four to eight hours of fasting. The flat film was repeated after thirty minutes of sucking on an empty bottle; the frustrated, younger subjects cried lustily for a part of this time. A third film was taken after an oral intake of 15 to 120 c.c. of milk. The results are tabulated in Table II. Figs. 1 to 4 are representative films.

The findings indicate that, contrary to popular opinion, air is not easily swallowed by infants except during deglutition. The films invariably revealed no change in the stomach gas pattern following thirty minutes of sucking on an empty bottle, but the stomach routinely appeared filled with air after the ingestion of milk. In a few instances, the infant burped the air out before the third film could be taken, and there was minimal demonstrable roentgenographic change. The subject apparently swallowed two to three times as much air as fluid. The stomach of an infant was visualized following the injection of 75 c.c. of air which showed a gas bubble comparing in size to the gas shadow formed by ingesting 30 c.c. of milk (Fig. 5).

Another investigation conclusively demonstrated that the stomach gas was swallowed air rather than the result of food decomposition or diffusion. Three subjects were allowed to ingest a measured amount of fluid, and at a subsequent time the same amount of fluid was gavaged. Films taken following gavage of fluids did not reveal the characteristic air-filled stomach (Fig. 6). These findings confirm Soveri's investigations.[14]

From a theoretical standpoint, it is difficult to conceive of air entering the stomach of infants with each inspiration.[13] If as little as 0.1 c.c. of air was ingested with each inspiration, an infant with a respiratory rate of 36 would ingest more than 2,500 c.c. of air in each twenty-four-hour period, exclusive of air swallowed during feeding. Atmospheric air is 80 per cent nitrogen which is poorly absorbed by the intestinal tract, and swallowed air is largely passed as flatus.[15] Adults usually egest between 500 and 1,000 c.c. of flatus per day, and the gastrointestinal tract contains an average of 1,300 c.c. of gas at any one time.[16] The concept of continuous, inspiratory air swallowing in infants seems unreasonable in view of these figures.

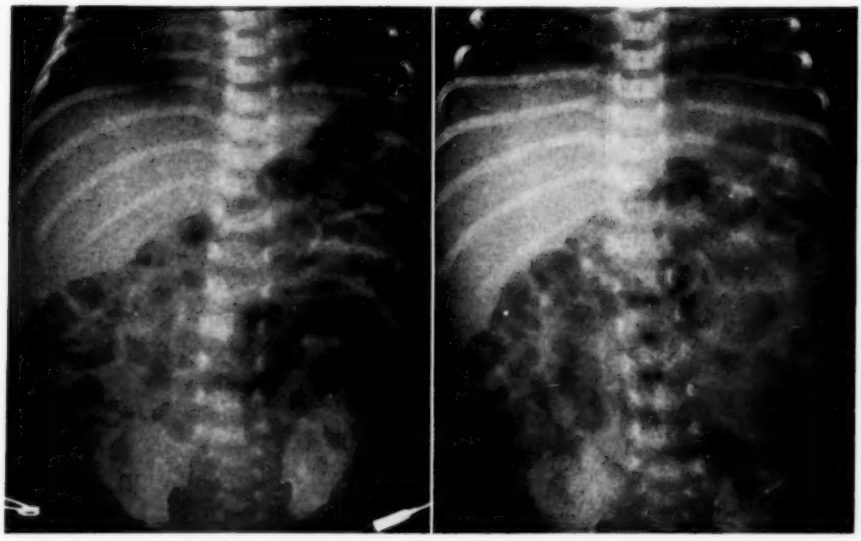
Gastric tubes were passed on three infants in the nursery, and the free ends were placed under water. In each instance there was an immediate bubbling of gas as the stomach emptied, since the intragastric pressure is a positive 8 to 13 cm. of water as is the intraperitoneal pressure.[16, 17] There was no further passage of gas through the water with expiration, and thus Leigh and Belton's[13] findings could not be confirmed.



A. *B.*

C.

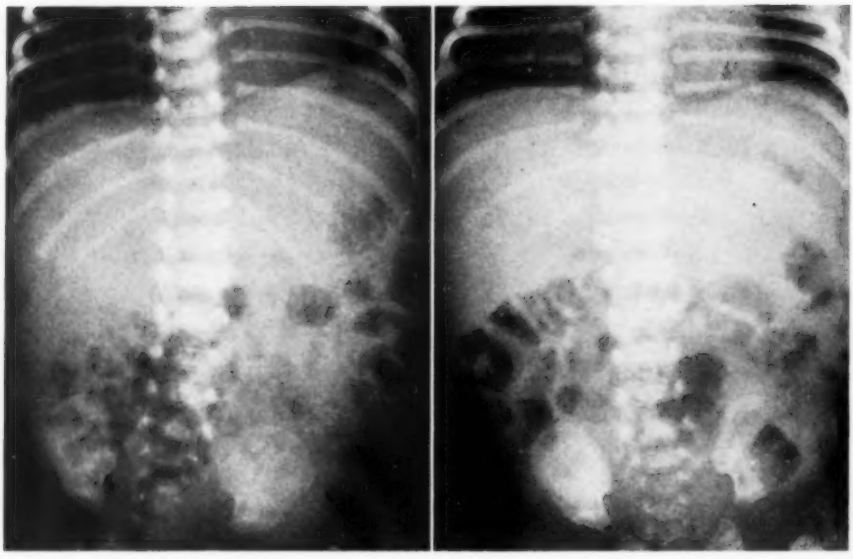
Fig. 1.—Case 4, Infant aged 18 days. *A*, Fasting film. *B*, After sucking for thirty minutes on an empty bottle. *C*, After ingestion of 45 c.c. of milk.



A. *B.*

C.

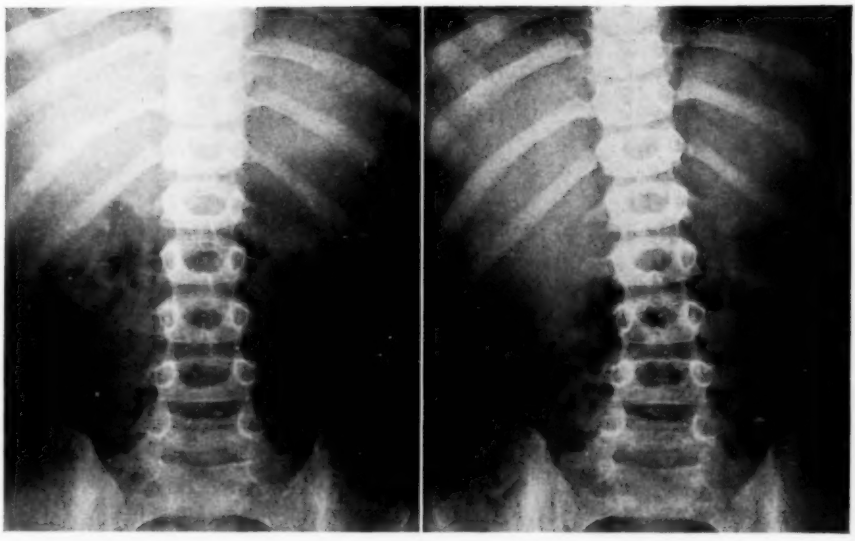
Fig. 2.—Case 5. Infant aged 21 days. *A*, Fasting film. *B*, After sucking for thirty minutes on an empty bottle. *C*, After ingestion of 30 c.c. of milk.



A. *B.*

C.

Fig. 3.—Case 6, Infant aged 1 month. *A*, Fasting film. *B*, After sucking for thirty minutes on an empty bottle. *C*, After ingestion of 15 c.c. of milk.

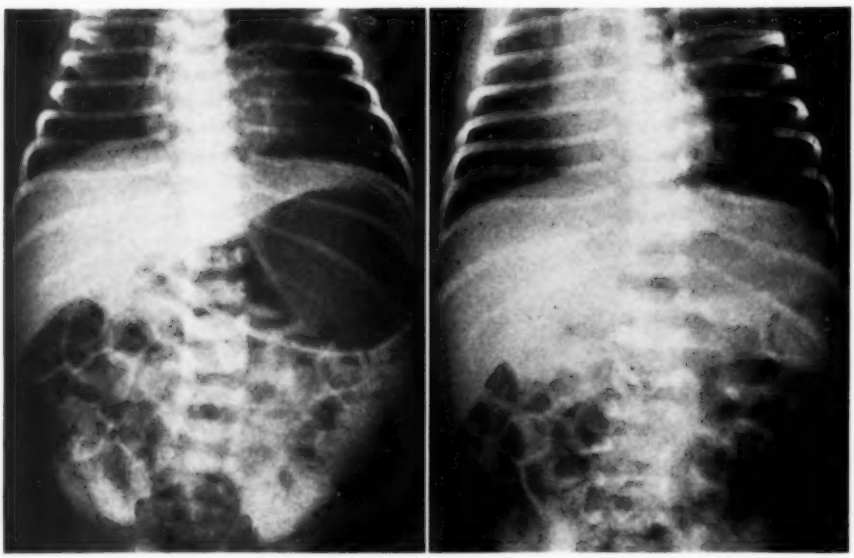


A. *B.*

C.

Fig. 4.—Case 13, Infant aged 6 years. *A*, Fasting film. *B*, After sucking for thirty minutes on an empty bottle. *C*, After ingestion of 120 c.c. of water in a few gulps.

Fig. 5.—Infant aged 5 months. Abdominal film following injection of 75 c.c. of air into stomach. Compare with Figs. 1, 2, 3, and 4.



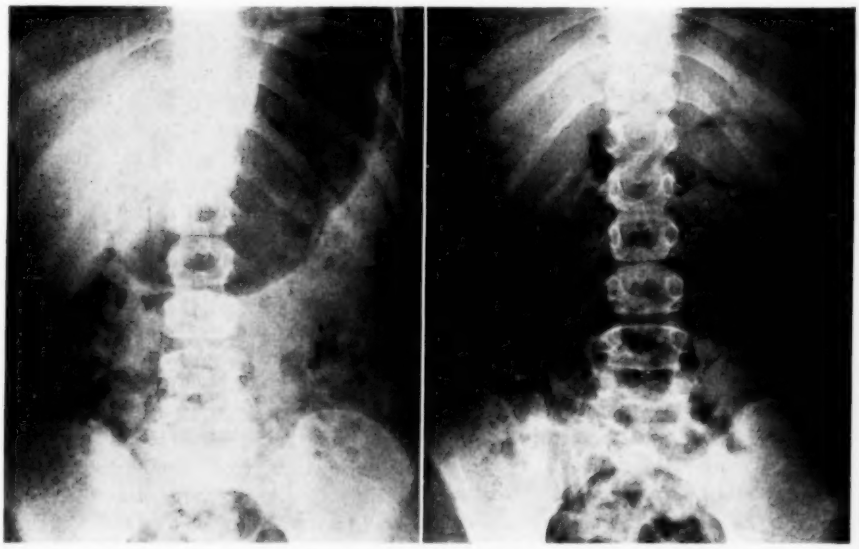
A. *B.*

Fig. 6.—Infant aged 21 days. *A*, After ingestion of 30 c.c. of milk. *B*, After gavage of 30 c.c. of milk.

DIFFUSION OF GASES

The role of diffusion in the development of distention has been adequately stressed. Diffusion of gases into and out of the gastrointestinal tract unquestionably occurs and apparently does so in a manner conforming to gas laws. Gas under different pressures on two sides of a semipermeable membrane will diffuse until equilibrium is established. That intestinal gases obey this law was shown by McIver and associates.[15] When air (CO_2 = 0.04 vol. per cent) was introduced into the stomach of experimental animals, CO_2 diffused into the stomach until the concentration was equal to that of the blood (CO_2 = 5.3 vol. per cent). Conversely, when air with a high percentage of CO_2 was introduced, CO_2 diffused out of the stomach into the blood until equilibrium was established. Dunn and Thompson[18] obtained the same results in experiments with human beings.

Anderson and Ringsted[7] brilliantly analyzed the problem of ileus from a theoretical consideration of the gas laws and by animal experimentation. They concluded that intestinal distention is due almost entirely to swallowed air. They also claim that the physical laws prohibit diffusion of gases into the intestines under the circumstances that pertain in intestinal distention.



A. *B.*

Fig. 7.—Child aged 8 years. *A*, Acute dilatation of stomach in an agitated child probably due to a sympathetic response. *B*, Normal film of same patient.

How does one explain gastrointestinal distention when swallowed air apparently is no factor? Wangensteen and Rea[4] produced an intestinal obstruction in a series of dogs by ligation of the distal ileum. A number of these animals were then subjected to esophagostomy with inversion of the distal end, thus excluding swallowed

air from the intestinal tract. Two of these animals developed tremendous distention, more marked than any of the controls. The only explanation of this gas is diffusion, since the chief gaseous product of food fermentation is CO_2 which is rapidly absorbed. It is also difficult to explain acute gastric dilatation on the basis of swallowed air only. Fig. 7, *A* is an abdominal film of a fasting 8-year-old girl who became extremely agitated when told that she was to suck on a nipple bottle for thirty minutes. The gastric dilatation evidently appeared in a matter of seconds. An abdominal film of the same subject, taken on another day when she was calm, is shown for comparison (Fig. 7, *B*). The sympathetic nervous system, which is predominantly inhibitory to the gastrointestinal tract, apparently played a role in this instance of gastric dilatation. Dragstedt[19] has discussed the sympathetic and vagal factors in acute dilatation of the stomach. The role of the autonomic nervous system in the production of gastrointestinal distention is worthy of further investigation.

Many questions concerning distention of the digestive tract remain unanswered. Despite the evidence that air swallowing takes place chiefly during deglutition, it has been shown that the newborn infant's stomach fills with air as soon as six minutes after birth, and subsequent films reveal the small and large intestine to be filled with gas.[20] It seems to be conclusively established that the gas in the intestines of newborn infants is swallowed air, because no intestinal gas is found in a newborn infant with an esophageal atresia. No diffusion of gases can take place from the blood stream into the empty intestinal tract in accordance with the gas laws.[2, 7] The rapid appearance of intestinal gas in the newborn infant may be a phenomenom peculiar to the first few hours of life. Perhaps the superior esophageal constrictor of the newborn infant is not as efficient a pinchcock as it is later in infancy and allows more air swallowing than one normally expects. The answer to this question must await further studies on the pneumodynamics of the digestive tract.

SUMMARY

Gastrointestinal gas is produced from food decomposition, swallowed air, and diffusion from the blood stream as established in previous studies on the subject. The x-ray investigations presented here were carried out to further evaluate the role of swallowed air in gaseous distention. These studies indicate that air is swallowed mainly during deglutition; little, if any, air is ingested while crying or sucking as is popularly believed. The suggestion that infants normally ingest air during each inspiration has not been confirmed, although air swallowing unquestionably occurs during the first few minutes of life. Further investigation of the behavior of intestinal gases is indicated, particularly the role of the autonomic nervous system in the production of gastrointestinal distention.

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SUBCUTANEOUS FAT NECROSIS COMPLICATING HYPOTHERMIA

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THE recent observation of an infant developing subcutaneous fat necrosis as a sequel to hypothermia prompts the following report. The reduction in body temperature had been induced to permit occlusion of the circulation and performance of pulmonary valvuloplasty under direct vision. A single recent similar report of infantile subcutaneous fat necrosis complicating hypothermia has appeared in the literature.[1]

Infantile subcutaneous fat necrosis, or sclerema neonatorum, was described in 1875 by Cruse.[2] Histological studies were made and reported in 1907 by Fabyan.[3] The infantile variety differs sufficiently from the adult form to warrant its description as a separate disease entity. In the adult, subcutaneous fat necrosis is often seen in an obese female breast following trauma.[4, 5] This is a single isolated lesion. Its borders are ill defined and gradually fade off into the surrounding normal breast tissue. By contrast, in the infant, subcutaneous fat necrosis characteristically is a generalized process involving multiple areas, often some distance apart. An etiological factor of importance in both forms of subcutaneous fat necrosis is generally agreed to be trauma.[6] Intense cold, however, is an additional factor capable of causing subcutaneous fat necrosis in infants.[1, 7] Thus, in infants subjected to hypothermia and the trauma necessarily connected with prolonged, difficult, surgical procedures, a favorable situation for the development of subcutaneous fat necrosis exists. Hypothermic states are not of the same etiological significance in adult subcutaneous fat necrosis. Fat necrosis, as yet, has not been reported in adults following hypothermia. Smith and Fay[8] in "refrigerating" considerable numbers of adult cancer patients did not report this complication. Collins, Stahlman, and Scott recently cited Langer's[9] belief that the propensity of the infant for these changes lies in the difference in chemical composition of the infants' and adults' subcutaneous fat. The melting points of the main constituents of human fat are most informative. Stearic acid changes state at 69.4° C., palmitic acid at 64° C., whereas oleic acid changes state at the relatively low temperature of 14° C.[10] Adults having a higher percentage of olein in their subcutaneous fat are thereby relatively well protected from solidification and necrosis.[1]

Fox's[11] comprehensive article ably describes the clinical and pathological features of infantile subcutaneous fat necrosis. This disease entity is generally thought to be a self-limiting, localized process, involving multiple areas of the subcutaneous tissue of the infant. Individual lesions vary from pea size to large areas two or more inches in diameter. The smaller lesions are firm, hard, freely movable nodules. Larger lesions are often softer, may excavate and become cystic. As entire thicknesses of the sub-

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cutaneous tissue are involved in the larger lesions they are more likely to feel fixed. The corium overlying these areas shows a faint bluish-red discoloration. The uncomplicated lesion is not tender and disappears spontaneously in several weeks or months. General health is not impaired.

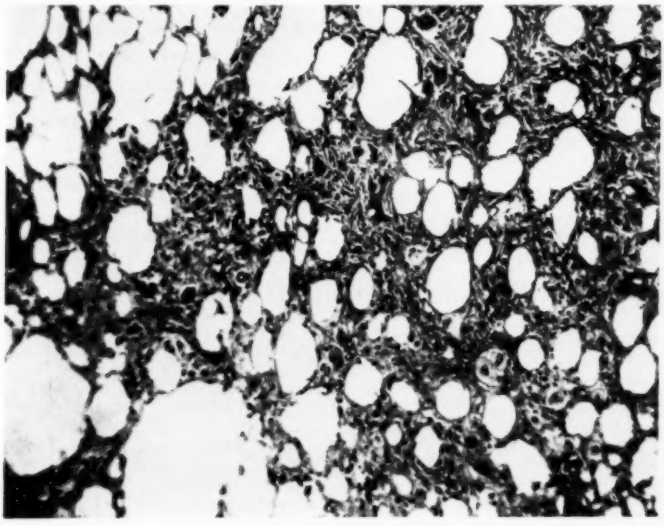

Fig. 1.

CASE REPORT

This 20-month-old white male infant was admitted to Fitzsimons Army Hospital after a period of outpatient observation. Past history reveals the infant to have been born two months prematurely, being cyanotic and edematous at birth. Growth curve was satisfactory until 9 months, when retardation became apparent. At 10 months syncope and convulsions developed.

Physical examination revealed a well-nourished, retarded, male infant, cyanotic even at rest. Pulse was 160, respirations 30, and weight 19 pounds. The heart was not enlarged. A systolic thrill and a Grade III systolic murmur, maximal, in the left third interspace, were present. P_2 was pure. The remainder of the physical examination was within normal limits.

Laboratory studies showed a hemoglobin of 16 grams and the hematocrit was 42 per cent. Electrocardiogram showed evidence of right ventricular hypertrophy.

X-ray revealed clear lung fields. The heart was boot shaped, with the transverse diameter being at the upper limits of normal. Fluoroscopy showed inconspicuous, quiet, pulmonary arteries. Diagnosis of tetralogy of Fallot was made and a shunting procedure advised.

Operation was performed under hypothermia on Feb. 23, 1954. The infant's temperature was reduced to 30° C. Palpation of the heart through the opened pericardium revealed enlargement of the pulmonary artery distal to the valve. A violent thrill was felt distal to the valve but not over the wall of the right ventricle. A jet lesion was felt in the pulmonary artery, accompanied by a bulgelike protrusion of the artery in this area. The aorta was large and displaced anteriorly and to the right. A diagnosis

of tetralogy of Fallot with pulmonary valvular stenosis was made and preparations begun for valvuloplasty under direct vision as described elsewhere.[12]

With the circulation temporarily occluded, the pulmonary artery was opened, and a typical pulmonary valvular stenosis noted. This was corrected by incising the diaphragm-like stenotic valve bilaterally, creating a bicuspid pulmonary valve. The lumen became quite adequate, the diaphragm being split back to the ring on both sides. The pulmonary artery incision was closed and circulation resumed without incident.

The postoperative course showed marked improvement in the infant's cyanosis and activity and seemed uncomplicated until three weeks following surgery when the infant was readmitted with an excavating lesion of the left buttock.

Upon second admission, history revealed that on March 10, 1954, sixteen days after surgery, a generalized purplish-red eruption had appeared over the trunk and a larger indurated lump developed in the left buttock. These generalized lesions were purplish-red in color, smaller than 1 cm. in diameter, and appeared to lie within the corium. Sloughing of the lesion of the buttock occurred, leaving an open ulcer with a necrotic core. The abdominal panniculus felt "knotty" and seemed to have clumped into small, hard, pea-sized masses. Over the course of several weeks, the generalized eruption cleared, and the small hard areas of fat necrosis felt in the panniculus showed progressive involution. Biopsy confirmed the diagnosis of subcutaneous fat necrosis (Fig. 1).

CONCLUSION

This case represents the second reported case of extensive subcutaneous fat necrosis occurring in an infant following induced hypothermia used as an adjuvant to cardiac surgery. We have observed repeatedly that infants, upon removal from the ice-water bath, show a diffuse firmness and solidification of the panniculus of the thighs and abdomen. This solidification is explainable on the basis of the lowered olein and the higher palmitic and stearic acid contents of the infant's subcutaneous tissue. No untoward results seemed to develop from the extensive subcutaneous fat necrosis which would mitigate against the use of hypothermia under similar circumstances in future cases.

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CONGENITAL ANKYLOSIS OF THE ELBOW

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THIS is the thirty-fifth case of congenital elbow ankylosis to be added to the literature. Most of these are reported by Romanus[1] who gathered twenty-four cases from the early European literature and added one of his own. His earliest mentioned case is that of a stillborn infant described in the Austrian *Yearbook of Pediatrics* for 1875.[2] In 1932 Acuña and Puglisi[3] described a case. Frostad,[4] in 1940, wrote of three instances in one family and two in another. Frankel[5] gave an excellent description of such a case and mentioned that three others in the same family of seven had the anomaly. Murphy and Hansen[6] and Lambert[7] added two more cases, the only ones previously described in the American literature. Prior to 1940 most of the reports describe the anomaly in one or both elbows associated with other congenital deformities. Ours is the tenth case in which the anomaly is isolated,[1, 3, 4, 5] the first in the American literature. It is of further unusual interest that consanguinity exists in the parents who are first cousins. They know of no other bony abnormalities in their background.

CASE REPORT

R. M. (No. 189352-N11), a white female infant, was delivered on Nov. 22, 1953, by low forceps from the vertex position. She was the product of an uneventful forty-week gestation and the birth weight was 3,355 grams. The mother was 30 years of age and had two normal babies from her two previous pregnancies. Her blood Wassermann, blood counts, and urine examinations were normal and, with the exception of multivitamins, no medication was taken.

General examination of the infant, including mental, neurological, and ophthalmologic evaluations, was normal except for the elbows which were ankylosed, forming an angle of 90 degrees on the left and 95 degrees on the right. Skull, chest, and sitting height measurements were within normal limits.

A roentgenographic study of the entire skeleton was made at 6 weeks of age. With the exception of the elbows, all of the bones and joints were found to be normally developed. The bone age was advanced, there being three carpal centers of ossification and four tarsal centers. This indicates a bone age of at least 6 months compared with the chronological age of 6 weeks.

The x-ray appearance of both elbows presented a grossly malformed articular relationship. In place of the normal humero-ulnar articulation, the proximal end of the radius formed a pseudarthrosis with a shallow cuplike depression in the anterolateral portion of the distal end of the humerus. The opposing ends of the humerus and radius were abnormally widened, the radius being larger than the ulna which is the reverse situation from normal. The soft tissue planes of both upper arms showed decreased, mildly atrophic muscles. Musculature development elsewhere in the body appeared normal. (Fig. 1.)

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The laboratory examinations performed were: blood counts, normal; urinalyses, normal; blood calcium, 11.75 mg., and inorganic phosphorus, 6.1 mg. per 100 c.c.; alkaline phosphatase, 5.4 Bodansky units. Intravenous pyelogram disclosed a normal urinary tract.

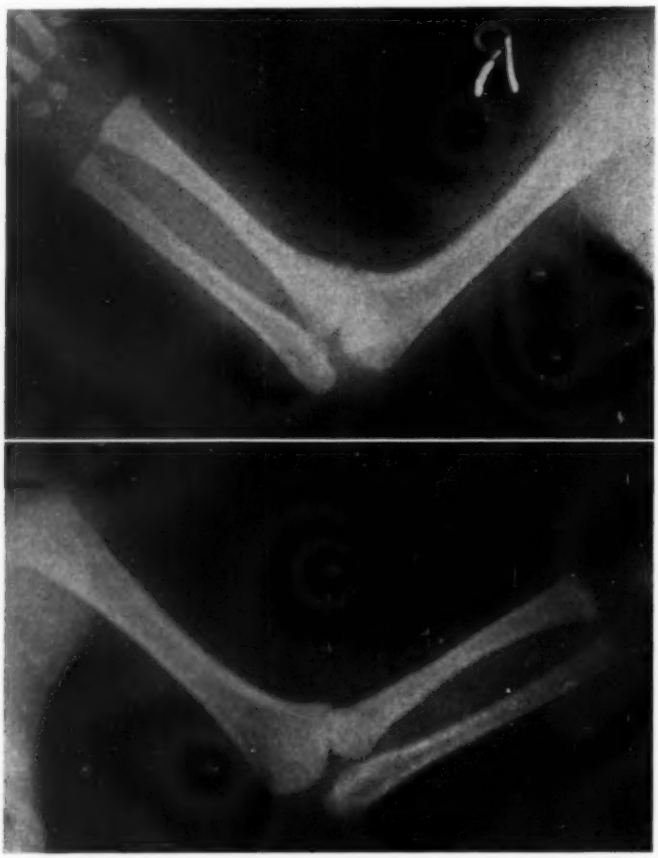

Fig. 1.—Right and left elbows at 6 weeks of age.

DISCUSSION

Congenital ankylosis of the elbows may be encountered in one of two forms: (1) as an isolated deformity and (2) in association with other anomalies. Of the latter group of twenty-five reported cases, the more common associated anomalies were absence of one or more bony structures of the hands; other synostoses of carpals, metacarpals, and phalanges; absence of ulna or of the opposite upper extremity; absence of one or both patellae; and shoulder girdle anomalies. All of those individuals of group (1), in whom the anomaly existed in isolated form,

showed bilateral involvement. Group 2 included eighteen cases of unilateral involvement.

In the large group described by Romanus we find three types of elbow ankylosis: (1) humeroradial synostosis, (2) humeroradio-ulnar synostosis, and (3) humero-ulnar synostosis. Several of the most recent cases are described under the terminology of humeroradial synostosis. In our case, the humerus and radius were not fused when first examined at the age of 6 weeks, giving an appearance of pseudarthrosis (Fig. 2). At the age of 6 months, both elbows showed advancing synostosis (Fig. 3). Most cases of humeroulnar ankylosis occur apparently when there is absence of the radius. The form of the anomaly may perhaps depend upon the age at which the patient is first observed. Judging from many of the illustrations, it is possible that our patient may eventually show synostosis between all three of the long bones of the arm.

The sex incidence is approximately equal, with twelve reported females, thirteen males, and the remainder not specified. According to three of the authors,[4, 5, 8] a marked familial tendency exists, suggesting a hereditary factor. The occurrence of this entity in four of seven siblings indicates, as Lambert has noted, that if hereditary, it depends upon a dominant trait. However, it is generally accepted that consanguinity favors the appearance of recessive traits,[9] of which our case is a possible example. Furthermore, the greater number of isolated cases over familial instances is consistent with the latter. It is obvious that there is insufficient evidence to come to any conclusion as to whether the fundamental cause is that of gene transmission or adverse environmental influence.

Fig. 2.—Left elbow at 6 weeks of age showing pseudarthrosis.

Although the cause of this anomaly is not known, two possible mechanisms could explain its development: (1) absence of the normal anlage for the elbow joint, or undersegmentation of the fetal cartilaginous ele-

ments which precede bone formation; (2) premature fusion of such elements, whether present in normal or more than normal number (oversegmentation).[7, 10] The accelerated bone age of the patient herein reported is conceivably in favor of the latter hypothesis.

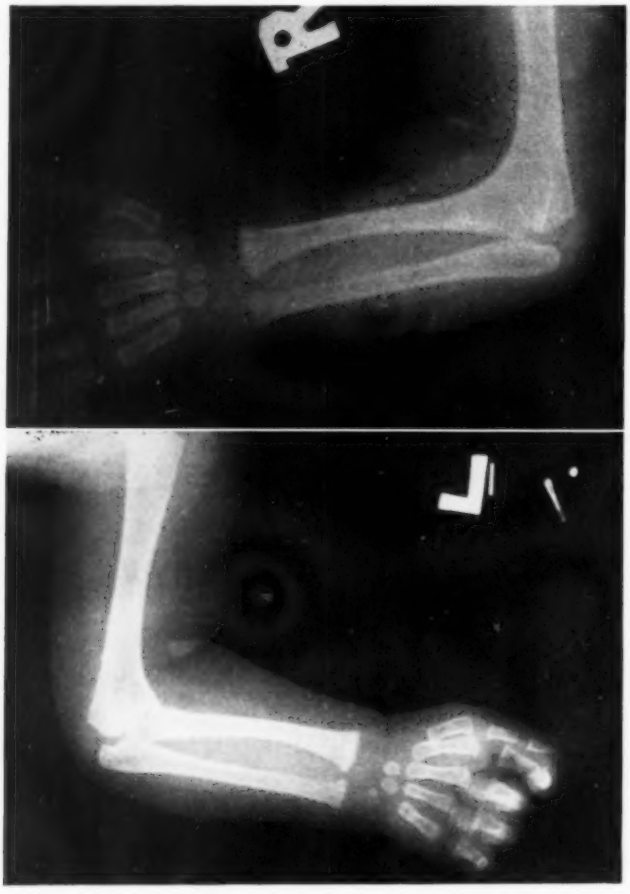

Fig. 3.—Right and left elbows at 6 months of age.

TREATMENT

Practically nothing is written regarding definitive treatment for this condition. Many cases of arthroplasty of the elbow are found in the orthopedic literature but the underlying condition treated is the result of disease or injury, never congenital. MacAusland[11] states that the ages at which arthroplasty is performed most successfully are between 19 and 45 years. Knight and Van Zandt,[12] who report an end-result study of forty-five cases of arthro-

plasty of the elbow from 1921 to 1948, make no mention of ankylosis on a congenital basis. They agree with MacAusland as to the best ages for operation because, if earlier, the damage may interfere with epiphyseal growth. This reasoning may not apply to cases of congenital ankylosis where no elbow epiphyses are present. Indeed, early operation in these instances might result in better development of arm musculature. One of the factors having to do with the question of surgical intervention is the eventual fate of the ulna, the growth of which may not be inhibited as with its neighboring synostosed radius, and this may result in a secondary deformity preventable by surgery. Long-term follow-up may cast some light on these problems.

PROGNOSIS

It is expected that with fusion and continuous osseous tissue from shoulder to wrist, as reported in this case, growth in length will be reduced since no epiphyses appear possible at the elbow. Apparently the adults with elbow ankylosis, as recorded in the literature, are well conditioned to their mechanical limitations of the upper extremity and lead useful and active lives.

SUMMARY

The thirty-fifth case of congenital elbow ankylosis is reported. It is noted that this is also the tenth case of bilateral elbow ankylosis not associated with other anomalies and the first such case in the American literature. A review of the literature and an analysis of those cases reported are made. Mechanisms of development and possibilities of treatment are discussed.

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Medical Progress

SOME PECULIARITIES OF AMINO ACID METABOLISM IN INFANCY AND EARLY CHILDHOOD

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THE metabolism of proteins and amino acids has always been of great interest to pediatricians. Early investigators, who were well aware that the growing child has a relatively higher nitrogen and protein demand than the adult, tried to study with the crude procedures at hand the complicated metabolic processes involved in the anabolism and catabolism of proteins.[30] In recent years, the development of new methods such as paper and column chromatography, microbiological assay, and radioactive and stable isotope techniques provides better avenues of approach to many of the old problems. With this fundamental information currently available, we can re-evaluate the facts gathered during the past fifty to eighty years.

In this paper some of the older studies on protein metabolism will be reconsidered in the light of the new concepts and ideas in this field. Pertinent investigations of the author will also be mentioned.

There seems to be little doubt that one of the limiting factors of growth of the child is the availability of the necessary amino acids in the proper concentrations and at the same time. This is even noted in adults in whom the levels of plasma amino acids are diminished when protein synthesis is accelerated, such as occurs after injury or antibody injection. A most interesting observation in this connection is the capacity of the placenta to concentrate amino acids in the direction of the fetal circulation. The first reports of this gradient are found in the paper of Morse. His studies were extended later by Hellmuth, Plass and Matthews, Sherman and co-workers. The most thorough investigations during this early period are those of Lichtenstein. Although they used methods (chiefly Folin's colorimetric procedure) which are not considered as good as present techniques, his findings of an amino acid gradient have been confirmed by recent invegstigators (for example, Crumpler and associates). From the limited amount of data in the literature and from our own studies, it seems clear that *the level of amino acid in the fetal blood is a function of the growth rate of the fetus in utero.* Thus Lichtenstein found that amino nitrogen was highest in the youngest and smallest fetus. Another observation favoring this concept was made by Christensen and Streicher. They found that the fetal cells in the rabbit are able to concentrate free amino acids to a far greater extent than maternal cells.

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The level of plasma amino acid of the mother is unchanged during early pregnancy. Although earlier authors (Plass and Matthews, Hellmuth, etc.) found no significant variation in the last trimester of gestation, Burt and Kimel, using current methods, have shown that the amino nitrogen is significantly *decreased* in the last months before birth. The only report which disagrees with this finding is that of Scontrino. The decreased values of Burt and Kimel are explainable by the rapid utilization of amino acids by the fetus at this stage of its development, resulting in the gradient mentioned previously. Simultaneously with the fall in plasma amino acids, a mild degree of amino-aciduria of the mother has been noted by Wallraff and associates. This excretion of amino acids must be the result of hormonal influence which, according to our experience with amino-acidurias in other comparable clinical conditions, produces an appreciable change in the amino nitrogen level of the blood. The effect of hormones on the amino acids will be discussed in a later article. The findings of Burt and some German investigators would seem to indicate that the fetus soaks up amino acids from the fetal circulation like a sponge. In keeping with this concept, these investigators report that the amino acid levels in the maternal blood are normal immediately after birth.

The findings just mentioned of the selective concentrations of amino acids in the blood of the fetus raise the question as to whether the placenta functions only by a redistribution of the solvent or whether it has an active selective secretory mechanism. A simple filtration process postulated by Pommerenke is not likely. Crumpler and co-workers have found by paper chromatography technique that there is a more or less uniform increase of individual amino acids in the cord blood. This seems to us surprising since the need for the different amino acids used in the protein synthesis is not the same in the fetus and the mother. We studied, therefore, by microbiological techniques (modification of Henderson-Snell method) the concentration of ten essential amino acids and of tyrosine in the cord blood of thirteen children.[111] Table I shows that the average plasma levels are higher than normal for infants in the first trimenon. The table also shows the range of the values.

Of all the amino acids studied, lysine showed the greatest increase in cord blood, and histidine demonstrated the next largest increase. In this connection it is of interest to note that Czerny suggested more than thirty years ago that lysine plays a particularly important role in the metabolism of nitrogen by infants. Also Neuberger and Webster have demonstrated that growing rats have a conspicuous need for this amino acid. Our findings should not be interpreted as corroborating these early experiments. Rather one would expect a low value of plasma amino acids which were being incorporated into tissues at a very high rate. In this connection, it is important to note that Borsook and Miller and associates have found a particularly rapid incorporation of lysine in the different proteins of the liver. It is reasonable to assume that the cause for the high lysine value in cord blood observed in our studies is the smaller rate of blood flow in the liver just before birth, than in the postfetal period. This is in accordance with the circula-

tory shunt known to exist in utero. Since we know that all lysine is transaminated by the liver, this shunt would seem to provide the most plausible explanation for the hyperlysinemia which I have shown to occur in utero. Turning now from lysine to histidine, one might postulate that its increase in the cord blood is related to the fact that the kidney is not functioning actively at this period. Such a hypothesis seems reasonable in view of our knowledge that histidine has the highest clearance rate of all amino acids.

TABLE I. AMINO ACID VALUES IN ADULTS, INFANTS, AND CORD BLOOD
(Average Values in Milligrams Per cent)

AMINO ACID	ADULT	INFANT	CORD BLOOD
Alanine	3.8	3.9	4.8
Arginine	2.1	2.2	3.3
Asparagin			
Aspartic acid	0.5		
Cystine	2.0 (?)	2.6	
Glycine	2.8	2.6	3.4
Glutamine	7.5		
Glutamic acid	1.1		
Histidine	1.7	1.8	3.4
Isoleucine	1.6	1.7	2.3
Leucine	2.0	2.3	2.5
Lysine	2.8	3.4	8.1
Methionine	0.35	0.3	0.5
Methylhistidine			
Phenylalanine	1.6	1.6	2.3
Proline	2.6		
Serine	1.4	1.3	
Taurine			
Threonine	2.0	2.3	2.8
Tryptophane	1.1	0.8	1.7
Tyrosine	1.4	1.6	2.3
Valine	3.0	3.2	4.9

It seems appropriate at this time to discuss the relation of amino acid metabolism to growth. Obviously an increase in the mass of the body of a growing infant occurs partly as a result of the synthesis of new proteins which participate in the growth of cells and formation of new cells. Attempts have been made to study this synthesis in vitro, using relatively simple models such as oligopeptids and enzymes (papain, cathepsin, etc.[19, 20, 41]) and glutathione synthesis.[18] There is no question that we deal here with marked endergonic reactions (ΔF at body temperature about +300 to +5,000 calories). There is also some evidence that high energy phosphate bonds participate in the synthesis of proteins in vitro as well as in vivo. We also have reason to believe that the glycolytic cycle and oxidation processes are the sine qua non conditions for formation of any protein. One must be a little careful in using these models in interpreting protein formation in the body. As a matter of fact no convincing evidence was obtained from in vitro and in vivo studies which suggests only an incorporation of amino acids into living matter. The difficulties of this complex problem are discussed in the elegant review of Borsook. Despite the difficulties of investigating protein synthesis, it is clear that growth itself is convincing enough evidence for protein formation.

There is no doubt that during infancy and childhood the amino acid demand is greater than in adulthood due to the growth of the organism. The few studies carried out on this subject are discussed by Albanese. Some of the values given in the tables are certainly quite high, but the author points this out himself.

Many efforts have been made to resolve the question as to whether the protein formation is due to an increased rate of synthesis, to a higher rate of breakdown, or both. One can quote data about certain specific reactions such as the slower rate of transamination processes in the embryonic tissues of the cat.[27] One can also note that co-enzymes I and II[12] and Cytochrome C[125] seem to have a lower activity in embryonic tissue than in the adult, without more basis, in fact. The importance of these enzymatic reactions in over-all process of protein synthesis has not been established.

A biophysical approach to the problem of growth has been attempted by Mayer and co-workers. They attempted to determine what they call "thermochemical efficiency" of growth using the following ratio:

$$\frac{\text{Increment in total heat content of the body}}{\text{Energy content of foodstuffs injested during this period}}$$

These investigators find a remarkable constancy of this ratio during the entire period of growth. Thus the ratio called "thermochemical efficiency" is about 24 per cent for energy and 17 per cent for protein.

Turning now from the individual factors concerned in growth to those which influence or control growth processes. Growth hormone of the hypophysis is certainly one of the most important of the factors controlling growth and one of the most interesting as well. Unfortunately, we know little about its mechanism of action. It could act in any one of several ways. First of all, it could influence the incorporation of amino acids into protein directly or indirectly by the stimulation of the energy-yielding processes which make protein synthesis possible. Second, it is possible that the growth hormone acts (as one of the "tropic" hormones) as a mediator. Third, the growth hormone could exert an effect on the different hormones such that a favorable situation for protein synthesis could result. It is certain that the optimal action of the growth hormone depends upon the normal function of all other endocrine glands, as well as on the presence of all necessary amino acids and an adequate supply of energy. It has also been established that the presence of the liver is essential for proper action of growth hormones.[39, 73] A number of studies have helped to clarify the function of the growth-promoting extract of the hypophysis on the body of rats. Lee and Schaffer, to our knowledge, were the first investigators to show convincingly that the administration of a special crude extract of anterior pituitary results in a deposition of proteins in the tissues of normal rats. Prior studies of Downs, Wadehn, and Bierring and collaborators are less convincing. Subsequent studies of Lee and Schaffer established the fact that hypophysectomized rats lose more proteins than do control animals on the same diet. Similar results were obtained by Young, Cuthbertson and other workers in this field.

When purified growth hormone became available, similar results were obtained by Li and associates and others. It is noteworthy that in the absence of the adrenal glands the growth hormone has no influence on amino nitrogen.[70] Thus, there seems to be little doubt that pure growth hormone fosters the deposition of protein. In addition, this hormone also increases the appetite of animals[135] and therefore an increase in the constituents of the body other than protein also have been noted. The amino acid levels of the blood have shown a decrease after the administration of growth hormone (Li and his co-workers as well as others).

It is not known whether the pituitary growth hormone is of major importance to intrauterine and early extrauterine growth. According to our experience with growth disturbances of childhood, it seems probable that the growth hormone is not of great importance to development during the first month of life. Growth appears to proceed during this period largely according to the intrinsic tissue and organ predisposition to grow. On the other hand, we see children remain as dwarfs as a result of a lesion in the hypophysis in their youth. The importance of other hormones for growth and protein synthesis can be seen in the different endocrine disorders during childhood.

Besides the influence of the growth hormone on amino acid metabolism, recent interest has been focused on the association of ACTH with catabolism and anabolism of protein. There is evidence in the literature that ACTH produces a negative nitrogen balance even in well-nourished animals or human beings. Li and associates and others have established the fact that ACTH raises the level of blood amino nitrogen. Schreier and Sattelberg have studied the influence of this hormone on children. They report that the increase in the blood level in the different amino acid studies is almost identical. Histidine and arginine are exceptions in that they show scarcely any increase. It has been suggested that the failure of the plasma levels of these two amino acids to be increased may be related (a) to the high activity of the arginase and (b) to the increased filtration rate of histidine. Another experiment which bears on the blood level of histidine is that of Grob who observed that the glucocortic hormones have a more or less specific function in the reabsorption of certain amino acids in the kidney. It seems probable that the metabolic effect of ACTH is due to the stimulation of glucocorticoid formation in the adrenals since these cortical hormones are known to produce identical changes.

Testosterone and other androgens have been shown to have a powerful action on protein anabolism.[56] Immediately after this hormone is administered, a temporary decrease in urinary nitrogen is detected invariably, as well as a diminished excretion of phosphorus, potassium, and sulfur. Within days or a few weeks after treatment has been instituted, the urinary nitrogen returns to the pretreatment level.[4] The claim of Shelton and Varden and Earle that testosterone benefits the growth and general condition of premature infants has not been confirmed.[50, 92] Like testosterone, the estrogens affect protein metabolism, but their action is not as pronounced. The mechanism by means of which the

genital hormones influence growth metabolism is not known.

The influence of insulin on amino acid metabolism deserves special consideration. It is a well-known fact that juvenile diabetics are, on the average, somewhat taller than normal for their age when the disease is first diagnosed.[60] Many of these children, especially those with poorly regulated diabetes, do not grow properly. A form of this dwarfism is known as Mauriac's syndrome. We have studied some aspects of amino acid metabolism in diabetes mellitus.[113] We had expected to find a difference in the behavior of glycogenetic and nonglucogenetic amino acids in view of the claims of Lichtwitz that protein metabolism in the diabetic proceeds in the particularly "economical" way. We studied the blood levels of essential amino acids and tyrosine in forty adults and ten children with more or less well-regulated diabetes and were not able to find any significant changes from normal values. In the comatous or precomatous state, many amino acids were significantly raised as is shown in Table II.

We observed that the urine of juvenile diabetics usually shows a slight or sometimes even a marked amino-aciduria due mainly to the increased urine output. It is known, of course, from our own observations as well as from those of others[73] that an increase in the filtration rate leads to a rise in urinary amino acids. We have observed, also, a marked amino-aciduria in comatous patients due, probably, to an overflow mechanism. We share the conviction of several outstanding workers in this field[57, 85] that insulin has no specific action on amino acids. Rather it seems that this hormone appears to be necessary to provide the energy for protein synthesis by means of the energy-rich phosphate bonds. In favor of this hypothesis is the fact that high blood levels of amino acids and amino-aciduria were detected in our patients only when in a state of insulin deficiency.

TABLE II. SOME AMINO ACID VALUES IN THE SERUM OF FOUR CASES WITH COMA DIABETICUM (Micrograms per Milliliter)

AMINO ACID	CASE I	II	III	IV
Arginine	29.0	27.8	24.0	32.0
Histidine	21.5	17.9	–	18.0
Isoleucine	45.5	34.2	31.8	19.6
Leucine	51.0	45.0	36.9	24.9
Lysine	37.6	33.5	40.0	38.0
Methionine	5.0	5.0	4.6	3.2
Phenylalanine	23.0	22.6	19.3	23.0
Threonine	21.0	23.3	21.8	–
Tryptophane	11.0	11.5	11.2	14.4
Tyrosine	20.0	23 8	18.9	16.0
Valine	60.0	–	45.0	40.6

The nonprotein components of the diet have a considerable influence on the metabolism of the protein fraction. For a discussion of the protein sparing action of carbohydrate and fats, we refer the reader to the review by Deuel and the paper of Schreier and associates. For this reason milk is a wonderful food for the growing organism, not only because it supplies proteins,

but also carbohydrate and fat, *simultaneously* to the tissues. (This is important in view of the "time factor" of Geiger and others.) An important point to discuss at this time concerning the nitrogen sparing action of the carbohydrate is what we call the "fructosomania" in Germany. Albanese and co-workers have claimed that fructose is superior to glucose in this respect. We were unable to confirm these claims in experiments performed on infants at the Universitäts Kinderklinik in Heidelberg and on rats at the Division of Experimental Radiology of the University of Rochester. Our studies on infants showed a somewhat different effect; namely, the slightly *increased* excretion of nitrogen-containing end products when fructose is fed alone; the babies did not gain weight as fast as those given glucose as the sole source of carbohydrate. Fig. 1 shows the results of our experiments in young rats. In this case, too, glucose is superior to fructose in these metabolic properties. The high urine volumes in the rats fed galactose were due to the rapid clearance of this carbohydrate by the kidneys. Interestingly enough, these rats showed an amino-aciduria similar to that found in galactosemia in infants.[15, 53] It is well known that the amino acid level of the blood falls after the injection of glucose. This drop is especially marked in the isoleucine fraction.[112] We were unable to show a significant decrease in the other essential amino acids. Similar studies have also been made by Munro.

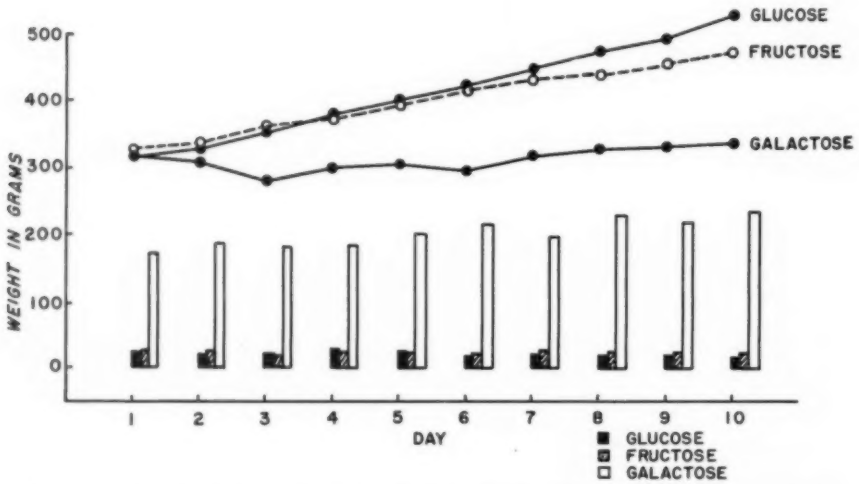

Fig. 1.—Weight curves and urine volume in groups of six rats on diets with monosaccharides.

Everyone is familiar with the observations of Rose, which indicate that if only one of the essential amino acids is missing in the diet, a negative nitrogen balance occurs. In this regard, it is interesting to note that the addition of a tryptophane-free hydrolysate to the milk diet of infants produces a very marked drop in the tryptophane level in the plasma. It is important to mention at this point, that the new-

born infant has been observed to have a well-developed capacity for digesting protein and for absorbing the split products from the gut.[93, 121] Studies on premature infants do not show us convincingly that these metabolic properties are fully developed. Werner, for example, finds that the activities of proteolytic enzymes of the pancreas and stomach are diminished in premature infants. This finding has been confirmed in Switzerland by Gschwind. In contrast to these observations Madey and Dancis report that the intestinal juice of premature infants has a normal proteolytic activity. Nevertheless, Magnusson, Agren and other Scandinavian authors suggest that in preparing diets for premature infants protein hydrolysates rather than undigested casein or other similar preparations should be added to human milk. In premature infants of older postnatal age, adequate capacity for digestion and absorption of cow's milk protein has been demonstrated by Gordon and associates. They were unable to prove a difference in the way these children handled human milk and cow's milk. There are no studies in the literature which deal with the digestive processes of the premature children shortly after birth.[121] We have undertaken, therefore, a study of nitrogen balance during a short period in three very young premature infants. Two of the infants weighed 1,750 and 1,800 grams and a third weighed 2,100 grams. On the fifth day of life in the case of the first two infants and on the twelfth day in the case of the last, they were placed in the "Stoffwechselschwebe." [This is a hammocklike bed (modified from Finkelstein) which permits a separate collection of urine and feces.] Our studies indicated that from 60 to 85 per cent of the total nitrogen in the food was retained. The addition of protein hydrolysate to the diet allowed even more nitrogen to be retained although up to 10 per cent of the amino acid of the hydrolyzate was excreted in the urine. We observed that the amino-aciduria noted when human milk diet was supplemented with protein hydrolysate was greater in very young premature infants than in more mature infants.

THE AMINO ACIDS IN THE BLOOD

The amino acid level in the blood of the full-term newborn infant decreases rapidly within about a week after birth and the values are the same as those observed in later life. In later infancy and early childhood, single determinations show a tendency of the amino acids to lie in the lower limits of the normal range of adults, especially when children are recovering from a serious disease process. This is presumably due to the fact that protein synthesis is more rapid under these conditions. This statement is not true, however, for the very young and for the very small premature infant. In these children the plasma amino acid levels are not likely to be low. On the contrary, we have found that a high percentage of the cases have significantly increased levels of amino acids. The increase is noted particularly in lysine and the cyclic amino acids (phenylalanine, tyrosine) and valine. These observations call to mind immediately the findings of Levine and co-workers who noted that a deficiency in ascorbic acid leads to

a disturbance of the intermediary metabolism of the cyclic amino acids of premature infants. This is related to the fact that vitamin C has been established as a coenzyme for oxyphenylpyruvase and possibly other enzymes which metabolize cyclic amino acids (for instance, Williams and co-workers). Like glutathione, vitamin C has a known oxidation-reduction potential which permits these enzymes to function. It should be mentioned at this point that adult patients with scurvy also may show a disturbance in tyrosine metabolism.[94] All of these findings seem to indicate that the metabolism of the cyclic amino acids is particularly labile in human subjects. The above abnormalities are presumably a manifestation of this fact. Another argument in favor of this concept is the frequency of inborn errors in the metabolism of phenylalanine and tyrosine.

AMINO ACIDS IN URINE

Since no studies have been made on the excretion of individual amino acids by infants, this seemed to us to be a fruitful avenue of investigation. After studying the urine of about fifty children from 5 days to 14 years of age, using microbiological techniques, we have concluded that within this range of ages, there is no *significant* difference in the mechanism of amino acid absorption in the kidney. If one compares the amino acids in one liter of urine from an adult and from an infant, a striking similarity is observed in the values of almost all amino acids studied. This is illustrated by the data in Table III.

TABLE III. THE AMINO ACID VALUES IN ONE LITER URINE OF INFANTS AND IN THE DAILY URINE VOLUME OF ADULTS

AMINO ACID	ADULT		INFANT URINE
	MICROBIOLOGICAL VALUES	COLUMNCHROMATOGRAPHY VALUES	
Alanine	30-100	46	30 - 40
Arginine	9- 25	10	4 - 10
Asparagin		43	
Aspartic acid	1	10	
Aminoadipinic acid		about 10	
Cystine	40-100	10	
Glycine	50-150	132	
Glutamic acid	0- 60	10	
Histidine	100-200	216	50 -150
Isoleucine	2- 15	18	2 - 8
Leucine	10- 15	14	7 - 15
Lysine	15- 45	19	6 - 20
Methionine	2- 8	10	0.5- 1.5
Methylhistidine		180	
Phenylalanine	9- 16	18	5 - 12
Proline	7- 15	10	
Serine	20- 30	43	
Taurine		156	
Threonine	15- 30	28	6 - 12
Tryptophane	15- 25		3 - 10
Tyrosine	15- 25	35	2 - 6
Valine	5- 15	10	4 - 9

Without going into details we should like to mention that the results obtained by microbiological techniques compare very well with those now obtained by the column chromatography of Stein and Moore. Our data as well

as those of Stein and Moore show that the amount of methionine excreted is less than one-twentieth of the value published previously by Albanese and co-workers. Similarly, the recent values for tryptophane are one-tenth of those previously reported by the same authors.

Since the infant passes more urine per kilogram of body weight than does an older child or an adult, he shows a difference in the ratio of amino nitrogen to total nonprotein nitrogen. Goebel was probably correct when he postulated that the amino-aciduria of early infancy is due to the high water content in the food. We should like to qualify this concept by stating this is probably the main but not the only cause of amino-aciduria, as we know that the tubular mechanism of the kidney is not fully developed in early infancy. The kidney is one of the organs with the so-called "Werdende Funktion."[86] Because of the incomplete development of the kidney, some young infants show a marked increase in histidine and lysine excretion and a few also have a high threonine excretion. (Schreier, unpublished results.) These three amino acids have the highest clearance rate of any studied in the human being.[101] This is borne out also by the studies of Eckhardt and co-workers who observed that, when hydrolyzates were administered to adults, histidine, threonine, and lysine were excreted in the highest concentrations. It is no wonder therefore that the kidney of the young infant has greater difficulty in handling these amino acids. Little is known about the mechanism of amino acid reabsorption in the kidney tubules. For a discussion of this problem the reader is referred to the outstanding book of Homer Smith and the author's chapter in the *Handbuch der inneren Medizin*. Of importance to the present study, however, is the known observation that the kidney of the infant is much more sensitive to slight changes in the blood amino acid level than is that of the older child or the adult. This has been clearly shown by our studies using protein and hydrolyzate tolerance. In adults and older children the amino acid excretion is scarcely affected by the protein content of the diet. In contrast, the urinary amino acids in infants and young children depend to some extent on the nature of the diet.[107] There is an extreme individual variation in the state of kidney development in infants.[98] It is not surprising therefore to find such a great range in the excretion rates of almost all amino acids that standard amino acid tables for individual age groups are not meaningful.

PATHOLOGY OF AMINO ACID METABOLISM

The great lability of amino acid metabolism in infants is clearly shown by the abnormalities existing in many pathological states. An example of a disturbance in amino acid metabolism is that observed in infantile diarrhea. Until recently, this disorder has been one of the most serious threats to the lives of young infants in Europe. In the German literature the terms "intoxication" and "toxicosis" are used to describe the state of severe infantile diarrhea with dehydration, collapse, and loss of consciousness. This is apparently comparable to the "acidotic state" of Rapoport and co-workers. "Pretoxicosis" is the less severe condition. All other forms of this illness are called "dyspepsia."

The first studies on nitrogen metabolism in infantile diarrhea were made by Keller. He investigated the ability of sick babies to form urea. He also studied the influence of malt extract on nitrogen retention. Two other teams of early investigators[76, 104] attempted to determine the amino acid excretion in urine using methods that are now known to be inexact. From these early studies it became evident that the severe forms of diarrhea were accompanied by an appreciable loss of amino nitrogen in the urine. These findings were confirmed about a decade later.[49, 80]

Table IV summarizes my studies on several amino acids in twenty-three children with uncomplicated dyspepsia (infantile diarrhea). Blood samples were taken immediately after the children were admitted to the hospital and before they had received any food except for tea in some cases. Since all determinations were done in duplicate, it was not possible to take enough blood to permit study of more than a few amino acids in each case.

TABLE IV. SOME AMINO ACID IN THE SERUM OF INFANTS WITH UNCOMPLICATED DYSPEPSIA (INFANTILE DIARRHEA)
(Micrograms per Milliliter)

CASE NO.	ARGININE	HISTIDINE	ISOLEUCINE	LEUCINE	LYSINE	METHIONINE	PHENYLALANINE	THREONINE	TRYPTOPHANE	TYROSINE	VALINE
1.	18	20	17	–	–	5	23	11	–	–	18
2.	14	30	32	50	58	10	36	29	20	25	36
3.	20	16	27	35	36	7	30	21	8	22	28
4.	–	–	22	–	36	7	–	–	13	22	–
5.	15	18	21	25	35	4	30	24	15	19	30
6.	14	19	22	20	32	4.7	32	23	8	16	26
7.	30	19	20	22	37	4	19	24	15	24	28
8.	19	21	33	28	40	8.6	29	33	29	24	28
9.	22	21	18	26	36	5.6	27	26	14	22	33
10.	24	20	18	26	36	5	–	29	17	23	–
11.	–	–	–	–	–	–	30	22.5	15	–	–
12.	30	19	20	21	31	4	24	20	15	–	–
13.	30	18	18	22	27	–	–	24	9	13	31
14.	–	17	20	35	30	5	–	29	7	19	–
15.	22	20	21	39	27	2.5	22	22	9	–	31
16.	35	19	19	36	31	–	24	24	–	13	–
17.	29	18	16	20	20	3.5	23	24	9	15	42
18.	32	18	23	20	33	3	31	24	9.5	17	40
19.	33	–	19	17	32	3.5	26	23	11	13	32
20.	43	–	18	20	31	4	27	18	15	18	30
21.	32	–	20	20	35	3	24	18	20	14	32
22.	–	–	23	25	50	5.5	24	–	14	–	44
23.	28	–	25	29	52	5.8	–	–	8.5	–	–
Average value	25.7	19.6	21.5	27.3	35.4	5.3	26.8	23.4	12.6	18.6	31.8

The average values of amino acids in Table IV show no striking change from the average of ten healthy infants of the same age. If there is an hyperamino-acidemia, it is probably due to the decrease in the water content of the blood, the existence of which was demonstrated by hemato-

crits done on the same blood samples. It should be noted that the range of values in the sick children is greater than that observed in normal infants. The change is probably a function of the severity of the illness. Thus our findings do not confirm those of the older investigators[9] who, using Folin's amino nitrogen method, claimed an amino-acidemia during illness. We observed, however, that in the more seriously ill children there is a significant increase in the plasma amino acid level which cannot be accounted for by the change in hematocrit.

Outspoken hyperamino-acidemia was found in two children with severe toxicosis.

It is a matter of great interest to consider which organs may be responsible for the increase plasma amino acid levels in children with severe illness. Our studies of amino acid metabolism in liver diseases may have a bearing on this point. Table VII shows a high degree of hyperamino-acidemia in two children with acute yellow atrophy developing in the course of epidemic hepatitis. The similarity of the amino acid pattern in both cases is striking. In contrast to these findings in seriously ill children, we have observed that children with uncomplicated forms of hepatitis usually show a normal or slightly elevated level of essential amino acids in the blood stream (Schreier and Sattelberg). When the plasma levels of amino acids are increased in these children, the greatest change occurs in methionine, tyrosine, phenylalanine, and lysine. These are the amino acids which, as previously indicated, are increased in infants with toxicosis. The

TABLE V. SOME AMINO ACID VALUES IN THE SERUM OF INFANTS WITH SEVERE DYSPEPSIA
(Micrograms per Milliliter)

CASE NO.	ARGININE	HISTIDINE	ISOLEUCINE	LEUCINE	LYSINE	METHIONINE	PHENYLALANINE	THREONINE	TRYPTOPHANE	TYROSINE	VALINE
1.	--	14	25	44	--	8.0	32	23.0	30	30	--
2.	34	20	32	39	60	8.5	34	31.0	25	19	59
3.	32	20	17	18	31	5.0	26	23.0	6	--	32
4.	50	32	17	18	31	5.0	22	27.5	10	14	40
5.	31	--	22	36	70	7.0	23	39.0	11	22	40
Av. value	37	21.5	22.6	31	48	6.7	27.4	28.7	16.9	21.2	42.8

TABLE VI. SOME AMINO ACID VALUES IN THE SERUM OF TWO INFANTS WITH TOXICOSES
(Micrograms per Milliliter)

CASE NO.	ISOLEUCINE	LEUCINE	METHIONINE	PHENYLALANINE	TRYPTOPHANE	TYROSINE	VALINE
1.	45	68	15.5	39	17	21	40
2.	38	70	13.0	28	21	22	60

TABLE VII. SOME AMINO ACID VALUES IN THE BLOOD OF TWO PATIENTS WITH ACUTE YELLOW ATROPHY OF THE LIVER
(Micrograms per Milliliter)

CASE NO.	ARGININE	HISTIDINE	ISOLEUCINE	LEUCINE	LYSINE	METHIONINE	PHENYLALANINE	THREONINE	TRYPTOPHANE	TYROSINE	VALINE
1.	120	46	28	58	100	28	85	39	35	37	38
2.	38	29	--	41	90	27	53	28	30	48	80

metabolic disturbances in both diseases are complicated as they involve not only amino acids but also carbohydrates. This is shown by the high blood levels of pyruvic acid.[115e] The similarity of the disturbance in amino acid metabolism noted in infantile diarrhea and liver disease suggests that liver damage in former disease could account for the increased amino acid levels. The decrease in glutathione values in children with severe infantile diarrhea, reported by Schriff, suggests a defect in the ability of the liver to synthesize oligopeptides. (In contrast to these findings, Italian workers claim high polypeptide values in infants with diarrhea.) Postmortem studies on infants dying of infantile diarrhea showed histological evidence of liver damage.[95] It seems reasonable to conclude that Finkelstein's "coma trophopathicum" is a special form of hepatic coma. From the metabolic point of view it is irrelevant to which of the following conditions or combination of conditions the liver damage is due: (a) absorption of biogenic amines and other toxic metabolites combined with hypoxia and severe loss of fluid, or (b) absorption of exo- or endotoxins of intestinal bacteria. In addition to these factors, acute starvation and fever may certainly affect the capacity of the liver to synthesize proteins or peptides from the available amino acids. It should be pointed out that the degree of derangement of protein metabolism in infantile diarrhea depends upon many factors in addition to the severity of the disease. Thus, the nutritional status of the patient, the nature of the pathogenic agent, and inherent tendency to specific metabolic reactions (such as cyclic vomiting) all play a part. This type of reaction may have something to do with the functional state of endocrine glands.

We should like to comment briefly on the importance of amino acid composition of the diet given children during bouts of infantile diarrhea. It is known that children on therapeutic diets frequently go into a state of negative nitrogen balance. This is particularly true for the diets used for infantile diarrhea. In several European countries there has been a trend in recent years to supplement all different types of "Heilnahrungen" with protein hydrolyzates. According to our own experience the addition of 0.5 to 1 per cent protein hydrolyzate may increase the speed of recovery in the child. Concentrations of hydrolyzate higher than 2 per cent may cause extensive edema, on the other hand, and even death of patients according to several published reports.

In addition to the disturbance of amino acid metabolism of sick infants one must consider the problem as it applies to the convalescent or undernourished child. The patient with a protein (amino acid) deficiency becomes more susceptible to secondary complications and recovery from the effects of the diseases is prolonged. It is obvious that children recuperating from illness need more amino acids than do those in good health. In addition to these conditions, the pediatrician occasionally sees infants who do not gain weight on a normal amino acid intake. In these patients, supplementing the diet with more proteins or hydrolyzates or both leads to normal growth and development of the

child. In these cases one must consider whether genetotrophic anomalies are present. Mitchell and Houlahan were the first to describe this condition and coin the name. Williams and associates have extended studies on this anomaly. A genetotrophic anomaly is one which is distinguished by a very high requirement for a special nutrient like a vitamin or perhaps an amino acid. Since such abnormally large amounts are seldom present in ordinary diets, these children may develop a deficiency or a toxic syndrome. The basic reason for the genetotrophic anomaly seems to be a partial genetic block. Such a block would evolve a heritable trait characterized by diminution (not a failure) of the ability to carry out some specific enzymatic transformation. In our case one could presume that the synthesis of nonessential amino acid is reduced or some transpeptidation or similar reactions are partially blocked.

We should like to return now to conditions other than liver disorders which are associated with hyperamino-acidemia. Elevated plasma amino acids have been reported to occur in diabetic coma[113] and in severe Basedow's disease.[58] Sandiford and coworkers and Schmidt have observed a slight increase in plasma amino acid levels in patients with leukemia and with severe infectious disease. The question as to whether liver damage could account for these findings in the latter conditions is, of course, not clear.

Turning now to pathological states in which a decreased plasma amino acid level has been reported, we find only one clinical condition in which this has been observed.[36] This condition is a nephrotic crisis. Our studies of amino acids in the plasma of five patients with severe lipoid nephrosis show that the values of tryptophane, isoleucine, and sometimes valine were decreased.[88] The composition of the isolated albumin in the urine of these patients and of the α and β globulin fraction (using paper electrophoresis) showed no changes from normal.[88, 115a] Thus we have not confirmed the theory that paraproteins are responsible for the pathological process in the kidney. Indeed, we have no evidence that they are present at all. This is true at least if one considers a paraprotein to be one which has a pathological amino acid composition. The claims of some investigators[1, 5, 46, 79] that such differences in protein composition exist can be due to inhomogeneous proteins used in their studies as well as the other factors in technique. Gitlin confirmed our observation of the identity of albumin in normal and nephrotic patients using immunological procedures.

No significant change in amino acid and nitrogen has been found in patients with the glomerular type of kidney disorder resulting in uremia.[105] We confirmed this for the essential amino acids. Alanine was found to be increased significantly in patients with uremia.[108] This is presumably due to the fact that the kidney has a high requirement for this amino acid because of ammonia synthesis. In concluding this section on the pathological states in which a disturbance in amino acid metabolism occurs, we shall mention briefly other conditions in which a hyperamino-aciduria is reported to occur. Increased excretion of amino acids occurs whenever the blood amino acid levels exceed the threshold due to the "overflow mechanism." In addition, hyperamino-aciduria is found in

kidney poisoning, for example, by phenol[122] or by uranium.[97] The increased excretion of amino acids in galactosemia[15, 53] seems to be due to the competitive inhibition of amino acid reabsorption induced by galactose. Vitamin D intoxication seems to affect the ability of the kidney to excrete amino acids. Finally we should mention that the acute exacerbations of progressive muscular dystrophy are characterized by an increased amino acid excretion.[8]

THE INBORN ERRORS OF PROTEIN METABOLISM

Some of the most interesting of the disorders of protein metabolism in human subjects are those observed in the so-called "inborn errors." These congenital anomalies are of interest not only to the pediatrician but to the biochemist as well. These disturbances of protein metabolism may be divided into four classes. First are the disorders due to failure of kidney function. Second are the generalized disturbances such as those due to disorders of amino acid metabolism found in Abderhalden-Fanconi syndrome. The third class comprises those syndromes in which one or another specific protein or protein fraction is missing. The fourth class is composed of those conditions in which the entire fractions of protein are absent. This is usually termed idiopathic hypoproteinemia.

An example of errors in amino acid excretion due to kidney dysfunction is seen in cystinuria. In this condition all of the amino acids containing two amino groups (diamino-monocarboxylic acids) are not reabsorbed by the kidney tubules in the usual way.[123] There may be other disorders of the same type in which groups of amino acids or individual amino acids are not handled properly by the kidney. Such conditions are particularly hard to diagnose because none of the clinical symptoms point to kidney dysfunction. In addition, there exists certain hereditary patterns in amino acid excretion which can be observed in the normal population.

The second class of inborn errors of protein metabolism are the generalized metabolic disturbances such as those seen in Abderhalden-Fanconi syndrome (cystinosis, cystine storage disease, etc.). The reader is referred to review articles in this field (Bickel and co-workers, Schreier) which consider the details of the pathogenesis of this puzzling syndrome. It should be mentioned that there is not always a significant increase in the level of most individual amino acids. The pattern of amino acids in the plasma is invariably abnormal. The total amino nitrogen, however, is not regularly increased. The recent observations of Freudenberg fits with my concept that the Abderhalden-Fanconi syndrome is a generalized disturbance in protein metabolism. It has not been established whether this syndrome is due to a defect in energy transfer or to the absence of specific enzymes. The deposition of cystine in all organs is due to the very low solubility of this amino acid. It should be emphasized that cystine is not the only amino acid found in the tissues. Freudenberg has recently demonstrated that tyrosine crystals are also present. In this hereditary disease the administration of salts of citric acid and of adenosine triphosphate seems to improve the clinical condition of patients by supplying energy for protein synthesis.

The third class of inborn errors of protein metabolism are those in which a specific protein or protein fraction is missing as a result of a genetic defect. Since we shall not go into the details of each disease, the reader is referred to the recent review by the author. We should like to enumerate the various diseases in this class, however. The best known is *hemophilia,* a condition in which the antihemophilic factor is lacking. Recently Bernfeld and co-workers have described an interesting peculiarity in the serum of members of hemophilic families, which can be seen on the electrophoretic pattern. This is the presence of $\alpha \times$ globulin. There seems to be a relationship between prothrombin consumption and the presence of $\alpha \times$ globulin in the plasma. The second condition, and one which is closely related, is *afibrinogenemia.* The blood of these patients contains almost no fibrinogen. Very recently, a new syndrome has been described. This is known as *hypoproconvertinemia* and is characterized by very low proconvertin levels in the blood. A third disease syndrome in the same class is *Wilson's hepatolenticular degeneration.* The missing protein of the blood in this particular disease syndrome is the blue copper-containing ceruloplasmin[81] which has a molecular weight of about 151,000 and a copper content of 8 atoms per mole or 0.39 per cent. At least decreased levels of ceruloplasmin in patients with Wilson's syndrome was first established by Scheinberg and Gitlin and has been confirmed by Bearn. Whether the absence of this protein can explain the entire symptomatology of the disease is still a matter of speculation. Interestingly enough, patients with hepatolenticular degeneration usually show a marked hyperamino-aciduria. A third disease in which a protein or protein fraction is absent is *hypophophatasia.*[91] In this syndrome the alkaline phosphatase appears to be absent or decreased and this results in defective bone formation. In recent publications Sobel, Clark and co-workers, and Schneider and Corcoran have added a few new cases to existing lists of this rare clinical syndrome. The fifth disease in this category is added somewhat tentatively. There is the *acatalasia*[54a] or *Takahara syndrome,* a disease which has been described in only thirteen Japanese patients. The symptoms of this disease syndrome are limited to an alveolar pyorrhea. The characteristic feature of the disease was that no catalase is detectable in the blood and tissues of the patient. In the absence of catalase, there is prolific growth of hydrogen peroxide producing bacteria in the mouth and this results in the destruction of teeth and alveolae. A further study of the biochemistry of this disease is necessary before it can be definitely classified.

The fourth class of inborn errors of protein metabolism are the *idiopathic hypoproteinemias.* As has been mentioned, a characteristic of this disease is that entire fractions of protein are absent. In some cases reported in the literature several of the plasma protein fractions are diminished.[22, 54, 61, 83, 99, 103, 127] Other reports indicate that only the gamma globulin is absent[23] or almost entirely absent,[124] or that albumin is missing.[11] Bound and Hackett have observed an infant with highly increased amino-aciduria and hyperamino-acidemia. Several cases

of acquired hypo- and disproteinemias without kidney dysfunction have also been reported.[52, 134] In order to make a diagnosis of this disease syndrome, careful study of the entire family is necessary. There is no plausible explanation for the pathogenesis of these anomalies.

The fifth and final inborn errors of of metabolism are those concerned with the defective handling of phenylalanine and tyrosine by the body. These conditions include (1) albinism, (2) alkaptonuria, (3) oligophrenia phenylpyruvica (phenylketonuria), (4) tyrosinosis. In the first condition the enzyme tyrosinase, which is necessary for the formation of melanin, is not present in the skin.[38a, 64] In alkaptonuria, the enzyme homogentisinase is lacking,[115d] whereas in phenylketonuria there appears to be little if any phenylalanine oxidase in the liver.[59, 129a] In this last disease the pathophysiological mechanism may be somewhat more complicated as is shown by the recent publication of Boscott and Bickel who detected not only the presence of phenylpyruvic acid but also the presence of para-oxyphenyl-pyruvic-lactic and acetic acids. Whether the tyrosinosis[75] is really an inborn error became somewhat doubtful when Felix found the pattern of this disorder in splenectomized patients with liver cirrhosis and hepatitis. The so-called erythrogenesis imperfecta[25, 32] seems to be due to a not yet well-characterized disturbance in the tryptophane metabolism according to studies of Altman and Miller.

CONCLUSION

Best and Hartroft have shown that young rats kept for only a short time on a choline-free diet develop later malignant hypertension. This seems to be the proof "that often fatal pathological changes during adult life may have their origin in a very short period of dietary abnormality in infancy." That means that in infancy and early childhood the foundations are laid down not only for the later growth and thriving but also for a healthy old age. We feel that it is the scientific and practical task of pediatrics to lay this base in the best possible manner. Therefore, the knowledge of the protein metabolism during this period is of utmost importance.

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Psychologic Aspects of Pediatrics

STATUS OF MENTAL HYGIENE AND CHILD GUIDANCE FACILITIES IN PUBLIC SCHOOLS IN THE UNITED STATES

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IN 1950 a research project was started at Columbia University in the Department of Psychiatry as a preliminary investigation in an attempt to ascertain how many and what kind of child guidance clinics and mental health facilities exist in public and private schools in the United States. To this end one thousand sets of questionnaires, and in some cases personal interviews, were used to acquire information from public and private schools† selected randomly within each of the forty-eight states.

The first purpose of the questionnaire was to obtain data in regard to the number of children recognized as:

(a) Emotionally disturbed
(b) Socially delinquent
(c) Manifesting a combination of emotional disturbance and delinquent behavior

The second purpose was to assess quantitatively and qualitatively the resources presently available for dealing with such personality problems in children, and the general mental hygiene concepts in schools, as well as the resources estimated by school officials to be essential for helping children.

The third purpose was to develop a concrete program of child guidance clinics in schools.

On the basis of a relatively high return of 35 per cent of the questionnaires, constituting a school population of 2,540,888 children, the following preliminary findings were among those obtained in this national survery:

1. The various schools reported a range of 60 per cent to 0.6 per cent of children as emotionally disturbed and in need of psychological help. Though this is a wide range, the returns indicate that about 10 per cent of school children are emotionally disturbed.

2. In 80 per cent of the schools, mental hygiene problems are not discussed in the classroom.

3. In 20 per cent of the schools, mental hygiene personnel give talks to the children. Of this group, however, less than half use specialists (psychiatrists, psychologists, and psychiatric social workers), indicating that about 85 per cent of the schools do not provide such a service by trained mental hygiene personnel.

4. There is a sharp discrepancy (a ratio of 1:4) between the presently available mental hygiene facilities and the need estimated for adequate handling of emotionally disturbed and/or delinquent children in schools.

5. Seventeen per cent of the schools reported that they had no mental hygiene services whatsoever available.

6. Fig. 1 (comparison of mental hygiene personnel existing and needed in United States public school system)

Part of this paper has been given at the meeting of the American Orthopsychiatric Association in Cleveland, 1953. Part of this paper has also been given at the meeting of The League for Emotionally Disturbed Children, January, 1954, in New York City.

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†The present report deals only with public schools.

reveals the outstanding disparity, in all areas surveyed, between facilities presently available to the schools and what the school leaders consider necessary to meet their needs. This is true without exception. The only area in which existing facilities even approach the need appears under the title of counselling teacher. This vague, undefined category which so many school systems have listed seems to be regarded by school administrators as a professional discipline on a par with little or no consideration for their qualification for this highly specialized kind of work. Only in a few cities, particularly where a child guidance clinic is working in a school setup, do we find that the counselling teachers have obtained some insight into personality behavior. Elsewhere their orientation is largely that of teacher training schools which most often seem to place disproportionately greater emphasis on discipline, order, and high marks than on social and emotional growth.

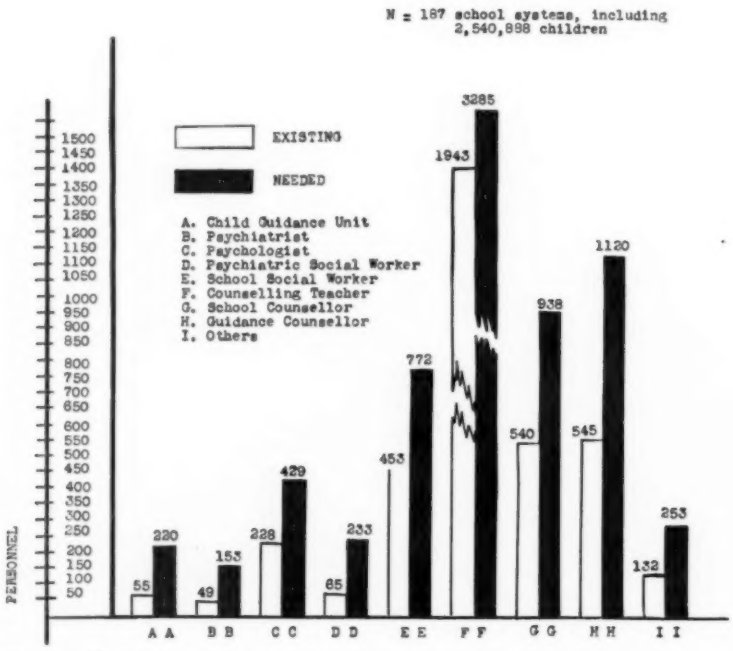

Fig. 1.—Mental hygiene personnel in United States public school systems.

the disciplines in the standard psychiatric team. From our responses and personal interviews, however, it is apparent that in almost all cases the counselling teacher is a "makeshift" mental health resource—the persons who are classified as counselling teachers have not been trained in psychodynamics or therapy techniques at any level; they are largely teachers who have been pressed into service with

7. Column A, which presents the need and existing personnel in the area of child guidance units, indicates that four times as many of these units as exist are needed.

Column B (psychiatrists) shows the need to surpass the existing number by a ratio of 3:1.

Column C (psychologists) reveals that though the absolute number required exceeds that of the psychiatrist

and social worker, when viewed on a relative basis only about twice as many psychologists are needed as presently exist.

Psychiatric social workers (column D) are required in a ratio of 3.5:1 above what they presently have. Columns E, F, G, H, i.e., school social worker, etc., respectively indicate an absolute need for such personnel exceeding the psychological personnel. When these figures are examined relatively, it can be seen that a greater discrepancy exists between need and availability in regard to the professional psychological workers than in regard to the nonpsychological workers.

This can be more graphically seen in Fig. 2, where the columns are presented on a relative rather than on an absolute relationship. In both Figs. 1 and 2, the first four columns represent the professionally trained psychological personnel, whereas the remaining columns represent the school personnel who substitute for clinicians under such titles as counselling teacher, school counsellor, etc. Thus it can be seen that, on a relative basis, the greatest need is for a child guidance unit, psychiatric social worker, psychiatrist, and psychologist, in that order. The relatively lower need above and beyond availability for the psychologist is explained by the fact that the psychologist is more frequently employed in the school systems at present, as a reflection of his traditionally closer relationship to the educational process. As such, he seems to be establishing a beachhead for the inroads by psychiatrist and psychiatric social worker.

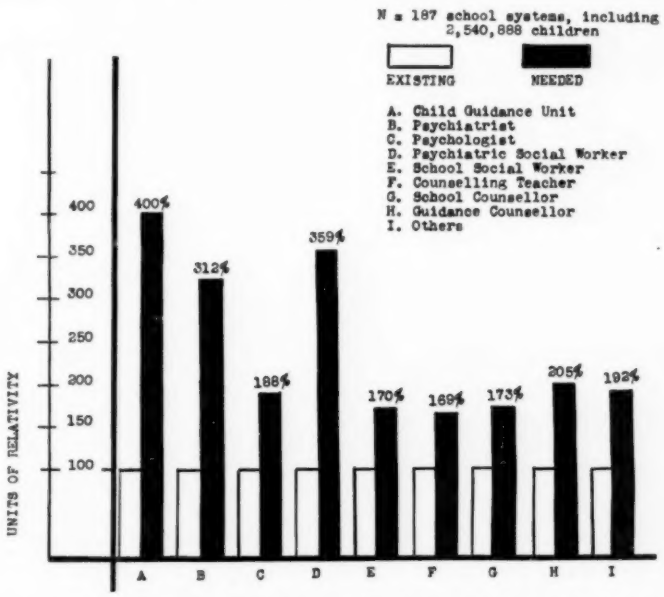

Fig. 2.—Comparison of expressed need for different types of mental hygiene personnel in United States public school systems.

For illustrative purposes, I would like to give some details of the child guidance facilities in a large metropolitan city. Though our sampling from this city is rather small, it nevertheless may indicate the lack of psychological personnel. This is a city

which is generally recognized as being well advanced in its physical plant, modern equipment and educational policies, and is highly aware of the emotional aspects as an important factor in the well-being of the child. This city probably represents the relative optimum in mental health facilities. Yet when we examine the figures, they indicate that the city needs a great deal more psychological personnel. The upper left circle of Fig. 3 represents the need for mental health personnel in the elementary schools in this city. Seventy-five per cent of this need is not met. Of the remaining 25 per cent, 4 per cent is handled by personnel not specifically trained for clinical service, i.e., counselling teachers, school counsellors, and the like; hence, only 21 per cent of the need for mental hygiene services on the elementary school level is met by trained personnel in a school system considered to be a leader in incorporating mental health concepts within its educational framework.

The upper right circle represents the need for mental hygiene personnel on the high school level in this city. In one respect, the need is more adequately met in high schools than in the elementary schools. Inspection of the circle shows that 50 per cent of the need is met on this level as opposed to 25 per cent on the elementary school level. Closer examination reveals, however, that this entire 50 per cent of available resources is composed of nonspecialists (counselling teacher, etc.). It would seem, then, that there are no facilities for treatment by trained personnel in the high schools of the city. This, however, is not the case. One reason why no professional personnel are represented in the high school is, by and large, because fre-

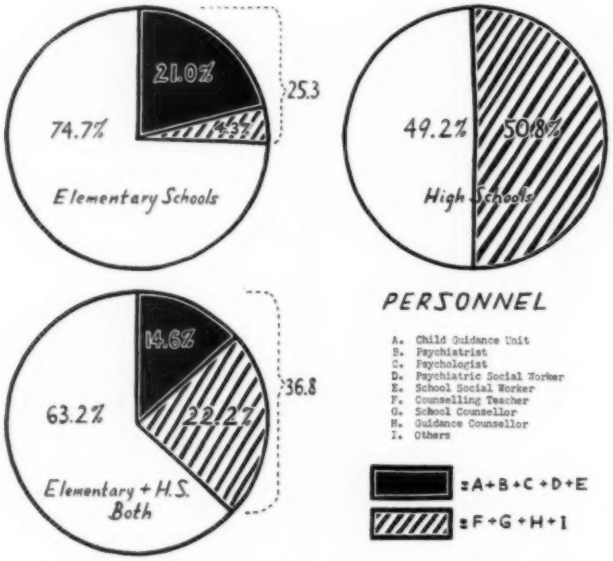

Fig. 3.—Per cent of need for mental hygiene personnel presently filled.

quently high school students are more resistant in seeking help. Further studies of this city seem to indicate that there are treatment facilities for high school children available there.

The lower middle circle represents the combined mental hygiene needs of both elementary and high schools. The combined tabulation reveals that 63 per cent of the mental hygiene treatment needs are not met. Of the remaining 37 per cent which are met, only 14 per cent are handled by persons trained specifically for this work.

This national survey of 2,500,000 children indicates that there is one psychiatrist for every 50,000 children, one psychologist for every 10,964 children, and one psychiatric social worker for every 38,461 children.

When we go through the estimated requirements for professional personnel by the school system, we find that they would consider adequate:

153 psychiatrists, i.e., one psychiatrist for every 16,340 children

429 psychologists, i.e., one psychologist for every 5,827 children

233 psychiatric social workers, i.e., one for every 10,725 children

The administrators of the United States public schools in our sampling seem, no doubt, to underestimate their need for professional personnel. It may be readily admitted that it is quite difficult to assess exactly these needs in a school system, since such an estimation depends on the standards of the teachers as to their insight, the number and quality of guidance counsellors, and the available mental hygiene facilities in the community. If, however, we suppose that a city has some mental hygiene resources for children, and that there is developed a system of educational and vocational guidance, we may indicate that a school system should have, ideally, one psychiatrist for every 8,000 children, one psychologist for every 2,000 children, and one psychiatric social worker for every 3,000 children.

Though our findings point up a great disparity between services needed and those available, this disparity may be even greater than our statistics indicate. We tabulated the exact responses to our questionnaires by the school superintendents, since value judgments could affect the validity of our findings. Where a response did not appear to be commensurate with other data on the questionnaire, a follow-up letter requested clarification. Invariably, the replies decreased the count of available mental health facilities. This may be illustrated by describing our experience with a large school system in a West Coast city. This school system, in reply to our questionnaire, indicated that it had seventy-three child guidance units. Based on the accepted structure of the unit consisting of at least one psychiatrist, psychiatric social worker, and clinical psychologist, we considered this figure high, and sent a follow-up letter. Their reply stated that they had ten full-time psychiatric social workers, two full-time psychologists, and ". . . the part-time services of three psychiatric consultants (totaling) twelve hours of psychiatric consultant time per week." This does not, of course, add up to seventy-three child guidance units.

Because the figure in this response appeared to be so unlikely, we were able to detect it, follow it up, and correct the tabulation. Similar discrepancies may have been recorded in other

responses, but because they were relatively minor we did not follow them up.

The findings here presented give a statistical picture of the mental hygiene problems and needs existing in our sampling of the public school systems. Statistics cannot adequately convey the human side of the picture. Fortunately, many heads of school systems, in responding to our questionnaire, included personal comments. These personal, spontaneous observations illuminate the statistics, and I shall cite a few of them.

Although most of these comments expressed interest in our research and generally represented a plea for help, some showed a remarkable lack of understanding of mental hygiene concepts. Only a few revealed indifference and lack of understanding. Among the latter was the response of a midwestern school superintendent to the question, "What kind of mental health services do you feel are required?" He replied, "I really do not know enough about it to have any definite opinion."

Such an answer, revealing lack of appreciation of mental hygiene principles, indicates a great need for training educational personnel at all levels in the understanding of personality dynamics. This faulty orientation is clearly illustrated by the school superintendent on the West Coast who wrote, "Our school system is rather strict from elementary grades up, and delinquency is not high here." This remark represents the old but apparently still vivid idea of "spare the rod and spoil the child" as applied to a school system. It ignores such basic concepts as the need of every healthy growing child for acceptance and expression. It ignores all that we in the field of mental health know of the relationship between frustration and aggression. Not too long ago our school systems insisted on uniformity and conformity; written assignments, for instance, were regulated by arbitrary standards and exact specifications, and pity the child who wrote his homework within margins slightly more or less than exactly prescribed. The end product of such constraint was, presumably, a neat child. But was he happy? Psychiatric studies of children have demonstrated the destructive aspects of repressive school practices, yet far too many school systems lag behind our knowledge in the field of mental hygiene.

Another West Coast school superintendent wrote us, "It is our opinion that a good teacher is better than a specialist in cases of minor maladjustment." While this is true in some cases, it must not be construed to mean that any kindly person can help emotionally disturbed people. In the back of the minds of many school administrators is that they, often unwittingly, consider psychiatric and psychological personnel as "outsiders" and feel threatened by them. Such a feeling may also in part have been brought about by some psychiatrists themselves, either in ignorance of basic principles of education or because of their being too impressed with their own specialty, or both. Also, because of conscious or unconscious resistant attitudes of many school executives, they often accept psychiatry on the surface only. Some of them may prefer to use community facilities fifty to one hundred miles away, rather than set up their own child guidance units. It would seem that those school

superintendents who strongly resist introducing psychiatric and guidance units into their school systems feel that this would be an admission of failure.

A southern school superintendent was asked, "Do you have mental health services?" and replied, "Yes, to a certain extent; nursing and medical services are available on call." Although this comment appears to show a lack of understanding of the difference between physical and psychological help for the children, it may indicate a resistance on the part of the superintendent against mental health services in all schools.

A high percentage of school system administrators, asked to list the mental health personnel they needed, gave priority to counselling teachers, nurses, attendance officers, deans, etc., over trained psychiatric teams of psychiatrist, psychologist, and psychiatric social worker. Many administrators are listed as mental health personnel individuals whose professional training does not, by any adequate standards, qualify them for mental health and guidance work.

A letter from a school system in the Great Lakes region shows this same lack of understanding and confusion as to the kind of emotional problems psychiatric teams deal with in daily practice. This letter, however, reveals sincerity and helplessness; it describes a situation in which trained workers can make a real contribution:

"Probably mental health services are required more often than we appreciate. It is rare (I believe) that psychiatric service is needed, or even clinical guidance service by a psychologist. It seems to me that the type of service which is most needed is that which will bring the home and the child into a closer and more harmonious relationship. One of our girls (ninth grade) just this morning told one of our guidance counselors that she hated her parents—and she was sincere. This girl hates or at least has no love for her ten brothers and sisters. Although this is an exceptional case, it illustrates my point. We, in school, could provide all the mental health services possible and it still would not handle the situation."

A child of the ninth grade, conscious of hating her parents, is a seriously disturbed child and in need of treatment. The hostility-guilt-anxiety cycle will sooner or later result in difficulties. This child has probably had some symptoms which have gone undetected until the ninth grade. Because she has been in school five or six hours daily, five times weekly, for the past nine years, we must ask why her disturbance was not observed much earlier. We know from our daily practice that this is not an "exceptional case," as the school superintendent believes; the exceptional aspect is that it did come to the attention of the school officials. Treatment of the child, as well as the family, appears to have been overlooked, though giving this child psychiatric care ought to have been within the realm of the school.

The letters from which I have quoted indicate some of the more serious problems which need to be faced in achieving an integration of psychiatry and education. These problems are primarily in the area of attitudes: lack of understanding, resistance, fear, indifference.

The majority of the spontaneous statements, fortunately, reveal a positive attitude toward this integration, but inability, because of inadequate funds, personnel shortage, and com-

munity lethargy, to effect integration. Here, too, both educators and psychiatrists have a real job to do. Here are some illustrative comments:

West Coast: "We may lose our clinic due to no competent psychiatrists being available locally and also due to a shortage of funds."

Rocky Mountain Region: "Probably every pupil has an emotional problem at some time. . . The laws of (this state) do not permit the schools to offer any kind of specific medical treatment."

Middle West: "Finance is always a problem; lethargy and lack of understanding on the part of the public is the greatest factor."

Southeastern Seaboard: "An increasing number of our children have emotional disturbances which we are attempting to help, although we have no one from whom we can get psychiatric advice. . . We have been hoping for several years to have a child guidance center, but we are making little if any progress. . ."

South: This school system indicated in their reply to our questionnaire that 25 per cent of their school population have emotional problems and the rate is increasing. Yet they indicated that they have no mental health services at present. Their response to "What mental health services do you need?" was, "The public is not ready and does not see the need."

Northeast: "We do not have any of the services you mention. We supervisors and classroom teachers are working on mental health problems to the best of our limited ability. . . This whole field presents our greatest problem. I think there are two basic reasons why resources are not available—lack of awareness of the need, and lack of funds in the departments where the awareness is known."

Southwest: This is from a school system which has *no* facilities: "Our children have severe problems. We need psychiatric help badly. Our town is full of neglected and insecure children, broken homes, and divorces. Our schools are overcrowded and understaffed. . . I would be grateful for any suggestion. . . The need is not understood and realized by our Board of Education. They see more virtue in a top-heavy athletic program."

It is quite interesting to note some of the answers received from large cities where child guidance service is attached to the school system, in contrast to services available only in the community. Both cities are located in an eastern state in large industrial areas. The one city has a public school population of 15,000 pupils and has attached to itself a child guidance unit consisting of one full-time psychiatrist, two full-time psychologists, one full-time psychiatric social worker, two full-time school social workers, and ten guidance counsellors. The other city, which has 35,000 children in its school system, has the use of one half-time psychiatrist, two psychologists, and ten school social workers. While the larger city reports in a given year only 139 new cases of emotionally disturbed children, the smaller city with 15,000 pupils and more adequate psychiatric services within the school system have between 150 and 200 new cases in the same year. In the latter school system mental health problems are discussed at the elementary, junior, and high school levels. The larger school system indicates it does not have any mental hygiene personnel who can discuss with the children mental hygiene problems. It is also quite illuminating that in the larger school system they had in one year about 2,300 interviews with the parents, while in the smaller school system they had that same year only about 600 interviews. These figures may indicate that there possibly was a great deal more emotional upheaval in the larger school system, which had developed only few psychiatric facilities, in con-

trast to the smaller school system which had developed better staffed services. The higher number of parent interviews does not reflect a greater awareness of the children's problems by the teachers, but rather that their problems became so pronounced that they had to talk with the parents repeatedly. This in contrast to the smaller school system where the teacher referred the children to the professional workers who dealt with their problems from then on.

On the whole, it may indicate the great difference of the quality of services when they are attached to a school system, in contrast to when they are dispersed througout the community without being directly tied to the school system. It is self-evident that in a school with child guidance services within its domain one finds more of an orientation toward mental hygiene concepts, more awareness of emotional problems, and more opportunity for educating teaching personnel in the basic concepts of mental hygiene.

Few doubt the importance of early child-parent relationships in the emotional well-being of the individual. We have here focused on the school because it is in the school that patterns of early life are crystallized and made visible, and here society has asserted its concern with the health and well-being of children.

We all know the size of the problem in terms of numbers of children either delinquent and/or emotionally disturbed, and we also know the lack of awareness of mental hygiene principles. Efforts to introduce psychodynamic u n d e r s t a n d i n g into the schcolteacher's armamentarium have met with resistance. The the parents themselves frequently feel threatened by psychiatry has intensified teacher resistance. Even classroom discussion of mental health problems, which often touch only the surface, is utilized in no more than 20 per cent of the reporting schools. The great discrepancy between recognition of need and availability of facilities indicates the serious situation American public schools face in dealing with the emotional difficulties of children.

Many school systems have attempted to meet the need by employment of guidance counsellors, or counselling teachers. How qualified are such personnel to handle the complexities of emotional upset? Professional training as presently given in schools of education and their own unresolved conflicts are serious barriers to the accomplishment of an adequate job by such counselors. The well-known findings of the Wickman study indicate that the orientation of school authorities can be at marked variance with that of the trained psychologist.

Diagnosing and treating children with emotional difficulties can be done only by those who have acquired skills specifically related to such work, that is, people in the clinical specialties. Teachers, counselling personnel, and other school officials must not divorce themselves from any interest in the mental health of the pupils. On the contrary, they are responsible for knowing when to use the clinic, for early recognition of emotional difficulties, and for helping to implement the program of therapy. Above all, in their awareness of mental hygiene principles lies the choice of whether the classroom shall be a place where children are encouraged to work out the problems of their day-to-day lives, to test out their concepts of socialized

living, or whether it shall be a place where disturbances go unnoticed, and symptoms are left to develop, frequently creating permanent scars, maladjustments or delinquency.

What feasible program of action can the United States public school systems undertake in order to achieve a fusion of the learning process with the emotional adjustment of both child and teacher?

One training center, the National College of Education in Illinois, has already undertaken a pilot course for teachers. A psychoanalyst, a psychiatrist, and a psychologist meet with the teachers to study the interaction of the personality of teachers and pupils. In general, the teacher-training program could be greatly enriched with the inclusion of more courses dealing with dynamic and group psychology.

Also such discussion meetings would give the teacher insight into transference and countertransference exchanges between the children and the teacher. Perhaps some thought should be given to conducting seminar meetings led by a trained psychiatrist on an interpretive level to assist in attaining such insight. Some research along these lines may be indicated.

An alternative or supplementary procedure until such time as enough clinicians are available to meet the need for psychotherapy in the school and to supervise the teacher's emotional interaction with the children, is to make more extensive personality screening a part of the teacher's entrance examination. At the present time, prospective teachers must pass the most scrutinizing speech tests, for example. Warm, stable, and mature individuals with an intuitive understanding of children often fail in the state teachers' examinations because of an almost imperceptible "dentalized 't'." More important would appear to be a psychological screening consisting of a comprehensive clinical interview and Rorschach examination, but this problem is extremely complicated and needs the most careful scrutiny.

Frequent consultation with the school clinician would help the teacher appraise the social-emotional climate in her classroom. Is the group interaction informal, democratic, healthy, and free? Do the children have opportunity to profit from emotional interaction and release of pent-up feelings? How are the children, as individuals, progressing in long-range personality growth? Which "problem children" need psychotherapy?

Then, too, how valuable are discussions with parent groups assembled according to the problems presented by their children: groups of parents whose children are bed-wetters, nail-biters, stutterers, behavior problems, etc.?

Thus mental health practices will gradually be woven into the fabric of the school day. The teacher will naturally synthesize her role of academician and group-leader therapist, freeing the children's capacity to learn by helping them toward personal and social adjustment. By the teacher's emphasis upon establishing full rapport with each child in her class, and by her structuring of a permissive classroom atmosphere, the children will have available to them a greater chance of achieving, first, a feeling of belonging, and then a feeling of status and worth. As Trow has pointed out: "Sometimes the teacher serves this end

by just being a friend, or he may provide, or himself be, an example with whom the child can identify."

We have for a long time let our children be concerned with learning about the three R's. Important as this is, it is now time for them to start learning about the fourth R—Relationship—that is, emotional relationship. It is essential for the child's healthy growth that he learn about himself and his own feelings toward his classmates and his teachers, and it is essential that teachers learn to understand the emotional attitudes of their pupils. Only through an integrated synthesis of the atmosphere of mental hygiene with the curriculum of the three R's can the educational process as well as the personality growth of the pupils be enhanced. The schools will have to accept responsibility for assisting children in integrating the aspects of feeling-doing-thinking, and thereby create the basis for adequate mental health.

But we cannot accomplish this by putting in a specialist here and another there, or by giving one hour weekly for some vague sort of guidance. What must be emphasized is that mental health concerns itself not only with one particular aspect of the human being, but with all aspects of his behavior. Teachers can learn from psychiatrists who in their turn can profit from their close collaboration with educators.

Though psychiatry is not a panacea for all ills and has its limitations, it has slowly worked its way into the fabric of our thinking. In the last few years the general hospitals have been opened to psychiatry and it has been included in the general curriculum of our medical schools. When so many agencies have seen the advantage of psychiatry, there is reason to believe that educators should give this matter their particular consideration, since the field of education influences and molds our future citizens in their formative years.

Education has a mind of its own and this has to be taken into consideration when we try to inject another process, mental hygiene, into the school system. Schools in general must be considered the most important preventive agency for mental ills and/or delinquency, and all personnel, from the superintendent to the clerk, should take cognizance of the mental hygiene aspect. School personnel would readily learn the value of mental hygiene concepts and contribute to the well-being of the children when child guidance clinics exist within the school system.

Having indicated the lack of understanding by a large part of the teaching personnel, parents, and children concerning mental hygiene concepts, one is compelled to ask, where and from whom can all these people become acquainted with these principles of mental hygiene? It would seem that one satisfying answer would be to have the Child Guidance units functioning closely within the school system, because they are not and should not be concerned only with the treatment of severely disturbed children, but also with the educational program. There is little doubt that sound leadership within the school system and within child guidance facilities would bring about a much-needed reorientation for the good of the schools and for the good of our children.

SUMMARY

In general it may be stated that the ordinary teaching process in the classroom, which primarily strives for learning, conflicts with the purpose of adjusting child and teacher emotionally to their tasks. Thus, while we must have education in mental health, we also need mental health in education.

Following these ideas to their logical conclusion, and based upon our present research study, we must state that there is in general a need to bring mental hygiene services into the school system in such a way that these services can be integrated into the functional structure of the total educational program. We may then be able to lay down basic principles which child guidance clinics in schools should follow in order to carry out the fundamental concepts of mental hygiene.

Accordingly, child guidance clinics in schools should be concerned with:

1. Study and treatment of emotionally disturbed children.
2. Selecting teachers on the basis of recognized personality criteria.
3. In-service training of teachers, to afford teachers deeper insight into psychodynamic interchanges taking place in the classroom.
4. Orientation of curriculum in classroom and curriculum development.
5. Close liaison with special educational and service programs such as speech development, attendance bureau, CRMD classes, etc.
6. Educational and community work, one of the aims being to integrate a parent's interests in the school system.
7. Professional training by providing opportunities for qualified young persons to gain experience in child guidance—by creating psychiatric residences, psychological internships, and student social work placements.
8. Research by maintaining a continuing program of developing and improving technique for integrating mental health with educational processes in school.

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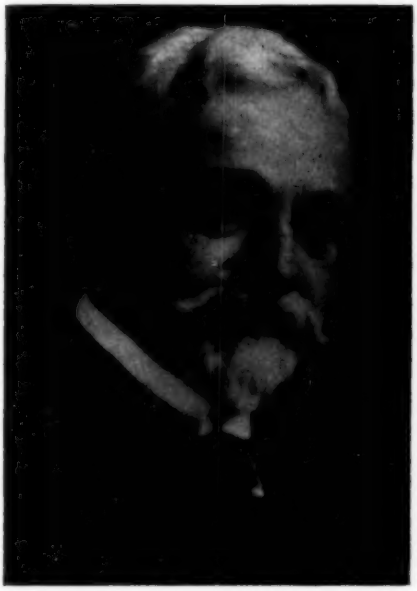
Pediatric Profiles

Henry Koplik
(1858-1927)



ALMOST every physician, the world over, is familiar with "Koplik's spots" as a sign of incipient measles, yet very few know who Henry Koplik was, when he lived, and what he stood for in the history of pediatrics. No American active during the last decade of the nineteenth century and the early years of the twentieth century did more for the advancement of pediatrics in the United States than Henry Koplik. Though his name will be carried down the years by his discovery of the pathognomonic sign of measles, his fame will rest not only on that discovery but on two other very important contributions—his founding the first baby health station and his emphasis on the laboratory in connection with clinical medicine. That his importance was recognized during his lifetime is well illustrated by the estimates of two of his contemporaries. Dr. J. J. Walsh opens his biographical sketch of Koplik in *The History of Medicine in New York*, published in 1919, as follows: "Henry Koplik, M.D., eminent New York physician, has had an enviable career. As a foremost specialist in diseases of children in this country, and former president of the American Pediatric Society, Dr. Koplik enjoys a reputation not only co-extensive with this country, but one that extends to Europe as well. As an exponent of Preventive Medicine, as discoverer of what has since been known as the 'Koplik's Spots,' and as the founder in America of the first milk depots known to the profession as the 'Gouttes de Lait,' out of which grew the universal idea of milk depots now in existence throughout the world, and as head of the Good Samaritan Dispensary for fifteen years, the largest pediatric clinic ever conducted in America, Dr. Koplik has had a career not easily paralleled in the lives of contemporary medical men, not only for its broadly beneficent and humane character, but as well for the distinctions attained in his chosen field of practice." In an obituary, written in 1927 for the New York Academy of Medicine, Dr. Emanuel Libman wrote: "Personally Dr. Koplik was

a man of distinguished appearance and dignified bearing. Whenever he discussed a presentation at a meeting, all eyes were at once turned to him, and all realized that they would hear a carefully worded and authoritatively expressed statement, based upon his own experience and his own views. In more intimate contacts one was impressed and attracted by his sparkling mind, his great knowledge and his goodly store of anecdotes and humorous stories. He was himself the kind of man concerning whom numerous anecdotes spring up. Some of these will no doubt be preserved."

Henry Koplik was born in New York City on October 28, 1858. He received the degree of A.B. from the College of the City of New York and M.D. from the College of Physicians and Surgeons of Columbia University in 1881 where he won the Harsen Prize awarded only to students of exceptional ability. Following an internship at Bellevue Hospital in New York he spent several years studying abroad in Berlin, Vienna, and Prague. This was long before Abraham Flexner made his famous trip to Europe, whence he brought back so many ideas that helped to revolutionize medical education in the United States. Koplik, too, was greatly influenced by his European training and later in life made numerous trips abroad during the summer months, visiting hospitals and clinics and exchanging views with the many great European pediatricians of that era, bringing back to America many of the innovations he had seen abroad.

On returning from his student years to New York in 1886 he started to practice and the following year was appointed attending physician to the Good Samaritan Dispensary, located in the lower east side of Manhattan, one of the most crowded slum districts of the city. Here he built up an extremely large outpatient clinic which became famous with its wealth of material as a model for the dispensary care of infants and children. With the financial help of prominent philanthropists, he started there what we now know as a baby health station. Not only were the infants examined, both the well and the sick, but proper formulas were prescribed and distributed to the mothers. It is interesting to read in the newspapers of the day and see what great publicity this novel form of prophylactic medicine received. When a drive was on for more funds for this rapidly growing institution, the Sunday edition of the *New York World* in June, 1899, devoted almost an entire page to pictures and descriptions of the clinic. The accompanying table, quoted from a leaflet distributed to obtain financial aid, is interesting to show the rapidity with which the new idea took hold and how the clinic grew.

RECORD OF FIRST TEN YEARS' WORK OF MILK DEPOT OF GOOD SAMARITAN DISPENSARY

YEAR	BOTTLES SUPPLIED	CHILDREN SUPPLIED
1889	7,000	137
1891	44,111	574
1892	57,371	700
1893	70,068	976
1894	70,705	720
1895	75,550	932
1896	96,311	766
1897	155,989	1,064
1898	298,674	1,204

From six to eight bottles of milk a day were dispensed per infant, depending on the doctor's orders. Six bottles sold for eight cents; the de-

posit on the bottle was three cents and on the rubber stopper was one cent. About 200 free bottles were dispensed daily and on Saturdays the number ran as high as 2,000. When one considers that the milk had to be kept refrigerated, that the formulas had to be prepared, that the bottles had to be cleaned and sterilized, and that careful records had to be kept of the financial side of the enterprise as well as of the medical condition of the child, one stands in awe of the man who could successfully manage such an undertaking. He must have been a genius at organization. Koplik has told the story of the foundation of this clinic in an article published in 1914 under the title "The History of the First Milk Depot or Gouttes de Lait With Consultations in America" (J. A. M. A. **50**: 1574, 1914).

It was also at the Good Samaritan Dispensary that the enanthem on the buccal mucosa of measles cases was discovered. The description of the pathognomonic "spots" first appeared in the *Archives of Pediatrics* published in New York in 1896 in an article entitled "The Diagnosis of the Invasion of Measles From a Study of the Exanthem as it Appears on the Buccal Membrane." Herein a long and careful description of the sign and its great significance as a diagnostic aid was clearly set forth, but curiously enough, the medical profession did not seem to realize its importance. A second article in the *Medical Record* in 1898 and then a third one in the *Medical News* in 1899 finally aroused physicians; publications here and abroad corroborated Koplik's findings and confirmed the great value and significance of his discovery. Under the title "Some Pediatric Eponyms. III. Koplik's Spots," W. R. Bett (Brit. J. Child. Dis. **28**: 127, 1931) gives an interesting account of this struggle for recognition.

Koplik's articles on his sign exemplify one of his most striking character traits, namely, his indomitable perseverance and his forcible will to carry through any undertaking he had once begun, regardless of whatever obstacles and difficulties might stand in his way.

Mrs. Bierman, Dr. Koplik's daughter, tells an amusing story of how, when her mother took her and her two brothers to Europe on a German steamer, one of the boys took sick and she asked the ship's doctor to have a look at him. This very pompous young physician demonstrated to her some lesions in the boy's mouth which he told her were "Koplikssche Flecken," a recently discovered sign of measles. There was considerable excitement when the doctor was told that the boy was the son of the discoverer.

Koplik's interest in the laboratory as an aid in the practice of pediatrics was probably acquired in Europe, for early in his career in New York he established a laboratory at his own expense in the Good Samaritan Dispensary. Here he not only did clinical pathology for the sick patients but also carried on original bacteriological research. Among one of his findings was that of a small bacillus obtained from the sputum of whooping cough cases and grown on media enriched with human blood. This he believed was the etiological agent of pertussis and was published as such in 1892. Referring to this, Emanuel

Libman, himself an expert bacteriologist, says, "At that time differential immunologic methods were not available, and for that reason a strict comparison with the organism of Bordet-Gengou cannot now be drawn. The bacillus of Koplik seems, however, to conform to that of Bordet and Gengou." In the days when this work was done, there were not many children's dispensaries in America where clinic and laboratory worked so closely hand in hand. Libman also says, "Because of his [Koplik's] interest in scientific pursuits, he early attracted the attention, admiration and support of such men as Adami, Jacobi, Osler and Welch." In the early part of his career he was very close to Jacobi. In fact, the latter entrusted to him much of the preparatory work for his classical monograph on diseases of the thymus.

As a clinician Koplik was a real master. He could size up a case in a few minutes, and when he had finished his physical examination, there was rarely anything that had escaped his acute senses. At a time when there was no x-ray to control clinical findings, the physician was much more dependent on auscultation and percussion in making diagnoses of intrathoracic conditions than he is today and he therefore became much more expert in the use of these diagnostic means. His delicate percussion of a young infant's chest was performed with the artistry of a pianist, and I recall his particular skill in diagnosing in the very young the presence of empyema, then a very common disease.

After some years as adjunct visiting physician to the children's wards of the Mount Sinai Hospital, Koplik was appointed attending pediatrician, a position he held for twenty-five years. His conducting of this service, where as intern and later as house physician I first had contact with him, gave one an excellent insight into his character and habits. In the hospital Dr. Koplik was a medical czar. His will was law and he brooked no interference. The men on the house staff were literally afraid of him, yet they respected his medical ability and his knowledge to such an extent that they welcomed the chance to work under him. Rounds were conducted with the greatest formality and woe to him who appeared late. He himself arrived at the hospital every day promptly at 8:30 in the morning, wearing a frock coat and a high silk hat. Koplik was a handsome man with pointed beard, a moustache, and bushy eyebrows overhanging a pair of flashing dark eyes. In what looked like holiday attire he made quite an impression and inspired people with real awe. After donning a white coat, he would appear on the wards where nurses and doctors immediately rose and rounds proceeded with military-like precision. I cannot recall his praising anyone on his staff but he did not hesitate to criticize and "call us down" if we were lax in any procedure or made some error in the handling of a case. He could make you feel very, very small. On one occasion he stopped at an empty bed and asked where the baby was who had been in the bed on the previous day. The child had been moribund with a hopeless disease and the house physician reported that he had died during the

night, to which Koplik replied, "Another death to your credit, Doctor," and moved on to the next bed.

The position of intern on the pediatric wards was an arduous one, for fifty years ago there were no technicians and all the clinical work was done by the interns. We had many cases of typhoid fever on the ward and Dr. Koplik made it a rule that during the height of the disease each child was required to have a blood count daily—quite a chore, which some of us performed by coming to the ward early and getting the counts done before breakfast. Our chief was meticulous about ward cross-infections and separated the beds of the typhoid cases from the remainder of the patients by movable stanchions connected by cords, so that their beds were roped off. In this way doctors and nurses were reminded to take the necessary precautions against spreading the disease.

How strict and rigid the ward routine was is well illustrated by the following incident: I was in charge of one of the pediatric dispensaries and one afternoon had a case admitted from the clinic to the ward for diagnosis. Next morning in the enthusiasm of youth, I went to the ward where I had recently been house physician, pricked the boy's finger, and took a blood spread to study at my leisure in my office. In some way Dr. Koplik was informed of this infraction of the rules and I was reprimanded by his saying to me in no uncertain terms, "I want you to know, young man, that every drop of blood in this ward belongs to *me*."

As is so often the case under such circumstances, there is bound to be a reaction at some time, when discipline breaks down and everybody has a good laugh. We had on the ward an infant suffering from tetanus who showed a typical "risus sardonicus." The child died and on the chart Dr. Koplik found a nurse's final note which even he could not take seriously: "The baby smiled and went to Heaven." As I recall, no one was reprimanded.

On his trips abroad during the summer Koplik investigated and reported in great detail the various measures used to prevent ward infections. New type of ward construction for children's hospitals in use in France and Germany that he approved of were introduced into America. He laid particular stress on the importance not only of the physical setup of the wards (cubicles, isolation rooms, etc.), but also of the necessity of having adequate and well-trained personnel. He constantly impressed his staff with the fact that every child must have a most thorough physical examination *before* he was admitted to the ward. Fifty years ago gonorrheal vaginitis in infants and young girls was a common, highly contagious disease which tended to very rapid spread through the hospital. Koplik laid down the most rigid rules and regulations for its control and as a result was able to keep his wards fairly free from this disease.

Besides his papers on ward hygiene and disease control, Koplik's clinical publications covered a wide range of subjects—poliomyelitis, cerebrospinal meningitis, the etiology of empyema, sporadic cretinism, streptococcus osteomyelitis, mongolism, pylorospasm and congenital pyloric stenosis, chronic arthritis, pneumonia and typhoid fever. Libman refers espe-

cially to the great value of Koplik's studies and publications on diphtheria in which he emphasized the importance of the differential diagnosis of the cases resembling simple sore throats and their rapid bacteriological diagnosis. In 1902 he published a book, *Diseases of Infancy and Childhood*, of which he was very proud. It went through four editions and he spent a great deal of time and effort in keeping it up to date, spending many evenings in collecting new items and subjects to be incorporated into the next editions.

As the result of his prominence in New York medicine, his practice grew by leaps and bounds and he was busy every day, seeing large numbers of children in consultation both in his office and in the city and its environs. He lived and practiced in the same house, a brownstone high-stoop house on east Sixty-second Street, where on a Saturday he commonly saw forty to fifty patients. A day when he only saw fifteen to twenty patients was considered a "bad day." He never had a physician to help him in his office. On a day when the office was busy, it was not uncommon to see women sitting on the steps of the house, some of them nursing their babies, the waiting room being too small for the crowd. Taxi drivers anxious to pick up fares parked in front of the house like at a hack stand.

I had an amusing personal experience which perhaps partly helps to explain this huge practice. A woman, who I thought was a loyal patient of mine, told me that she had taken her son to Dr. Koplik, although the child was quite well. Surprised at this, I inquired why she had done this, and was told that the grandmother believed "that every New York child should be seen by Dr. Koplik at least once."

As a consultant, Koplik was very helpful to the physician. By his looks and bearing and by his authoritative way of speaking and discussing the case he inspired real confidence in the patient's family. Occasionally he would inject a note of sardonic humor as in an instance when I called him in consultation to see a very sick pneumonia patient. At the bedside he inquired whether I was giving digitalis, and when I answered in the affirmative, he asked what brand I was using. I told him that I was giving Squibb's digitalis, whereupon he said, "You should use Upsher-Smith's." When I replied that I had never heard of that brand, he answered, seemingly quite seriously, "It is only used in consultations." One never quite knew whether he was laughing with you or at you.

With the onus of his writing and lecturing, his hospital work, and his huge practice, Koplik had little time for recreation or family life. He had no hobbies at all and devoted his entire energy to his medical life. He was deeply devoted to his wife, who was a great help to him and was always at his beck and call. Their social life was very limited; they had only an occasional dinner party and rarely went to theaters or concerts. Of their children only one now survives, a daughter, Mrs. Rosalie Bierman, of Norwalk, Connecticut. The younger son died at college at the age of seventeen, after his father's death. The older son, Lewis, became a physician and had an interesting though, unfortunately, brief career.

He taught for a time at Harvard Medical School, worked in pathology at the Mount Sinai Hospital, and having to give up practice on account of a heart attack, obtained a fellowship in public health at Johns Hopkins. He died at the age of thirty-eight.

In 1925, after leaving Mount Sinai Hospital, Henry Koplik gave his entire time to his practice and insisted on working in spite of a serious cardiac ailment which finally caused his death on April 30, 1927.

During his life Koplik had been elected to medical societies, both American and foreign. He was one of the founders of the American Pediatric Society and at one time was its president. His interest in child welfare resulted in his being appointed to many committees dealing with child health. "A source of great gratification to him was his appointment as a member of the Permanent Commission of the International Association of child welfare and gouttes de lait" (Libman).

In his will he bequeathed $10,000 to Mount Sinai for use in child care and $15,000 to Columbia University to found a scholarship for students of pediatrics.

Henry Koplik's place in the development of American Pediatrics is a significant one. His contributions were so varied that it is difficult to state which was of most value. Of great importance is the element of prophylaxis which he stressed in the conduct of his milk station. When one recalls how the infants of the poor were decimated by "summer diarrhea" and literally how many thousands of babies were saved by the clean milk and the prophylactic care they received at his hands, I think that this must be his chief claim to fame.

I wish to express my indebtedness to Dr. Koplik's daughter, Mrs. Rosalie Koplik Bierman, for putting at my disposition a collection of clippings and documents which were of value in compiling this article.

Murray H. Bass

Comments on Current Literature

TETANUS

AN INCREASING proportion of the patients treated for injuries by private physicians or in hospital emergency rooms comprises individuals who at some time have been actively immunized against tetanus toxin, and the question arises as to whether a booster dose of toxoid is needed, or an injection of antitoxin, if the interval since immunization has been more than a matter of months. A pertinent and interesting paper appeared in the October, 1954, issue of the *Annals of Surgery* by Stafford, Turner, and Goldman.[1] Data are tabulated which might be useful in answering this question. The Baltimore area seemed advantageous for such a statistical study, since in Baltimore the practice of immunizing infants and preschool children routinely with combined diphtheria and tetanus toxoid had been followed by a number of pediatricians prior to 1940, an immunization practice followed likewise by the City Health Department since 1950, and in the immunization of medical students at the Johns Hopkins University, and of students at the Johns Hopkins Hospital School of Nursing.

By a standard method[2] for detecting tetanus antitoxin levels, the comparative immunologic status of 175 persons was determined. Seventy-two of these persons had been in the Armed Services, and had received tetanus toxoid at least five years previous to the study. Seventy-three of the individuals studied had received tetanus toxoid within the five-year period just past, and thirty had never received tetanus toxoid. Initial serum determinations were made at the beginning of the study before the administration to each subject of 0.5 ml. of fluid tetanus toxoid intramuscularly, subsequent blood samples being taken at intervals over a period of about two weeks. The initial serum antitoxin level of all persons previously immunized indicated that if toxoid had been received five to eleven years before, a measurable level of antitoxin remained. Seventy-five per cent of this previously immunized group had 0.05 of a unit per milliliter or higher, the generally accepted protective level of tetanus antitoxin being considered as 0.1 of a unit per milliliter of blood serum.

Individuals who had received toxoid less than five years before the study showed, in general, a higher initial level, 93 per cent having 0.05 unit of tetanus antitoxin per milliliter. In this group the median level of antitoxin in the blood was tenfold that of the group whose last immunization toxoid had been received more than five years before. Thirty persons who had never received toxoid at all showed no detectable level of antitoxin in the blood.

Following the initial blood sample, the entire group of 175 was given 0.5 ml. of fluid tetanus toxoid, and the immunologic response to active immunization was followed by studying the antitoxin levels in the blood at specified intervals. In those of the group who had received tetanus toxoid injections less than five years previously, the response to toxoid was striking; within seven days there was a marked and rapid rise in serum antitoxin level, and at fourteen days, in nearly all these individuals, the serum level had reached 10 units per milliliter or more. This striking rise in antitoxin level began about the fourth day after the booster dose. In

contrast, no antitoxin could be demonstrated in the blood of fifteen of the persons who had never been immunized, even at fourteen days following the active immunization dose. The prompt response of the body to the introduction of tetanus toxoid in persons previously immunized demonstrates the efficiency with which the immune mechanism functions once exposed to an antigen sometime in the past.

A second aspect of the study conducted by Stafford, Turner, and Goldman concerned the pattern of serum antitoxin levels in patients following the intramuscular administration of 1,500 units of antitoxin. The usual levels, generally accepted on the basis of published studies, are 0.1 unit per milliliter of serum at twenty-four hours following this dose of antitoxin, 0.15 to 0.25 unit at four days, and back down to 0.1 unit in about seven days. Thus the time required to reach peak level following the administration of antitoxin is not very different from the four-day period necessary for the production of serum antitoxin in the immunized individual who is given a booster dose of toxoid. Moreover, some doubt has been expressed "as to the prophylactic value of one injection of 1,500 units of tetanus antitoxin."

In order to gain an impression of the efficacy of passive immunization with tetanus antitoxin, the authors undertook a review of the records of sixteen general hospitals in Baltimore, covering a period of twenty-five years. These records showed 169 cases of clinical tetanus infection. Of these 169 patients, 142 received no antitoxin at the time of the injury, and among the 142, 71 deaths were reported. Those who received antitoxin at the time of the injury numbered twenty-five, and of this number, thirteen died. The general conclusion would seem to follow that a significant number of patients with tetanus died in spite of receiving prophylactic tetanus antitoxin (1,500 units). It is of interest that the two remaining patients (of the 169) were individuals who developed clinical tetanus although they had been actively immunized. In both instances the illness was mild, and both patients recovered without the benefit of antitoxin.

Statistics available indicate that there are in the United States about 20 million persons who have been immunized actively against tetanus, either during childhood, or at the time of their service in the Armed Forces. Increasingly the question will arise as to what policy of treatment should be followed when tetanus is a possibility in such persons, who at some time have been actively immunized against tetanus. In summarizing their impressions following the two studies, the authors make these recommendations: "It is recommended, therefore, that in civilian practice a stimulating dose of tetanus toxoid alone be administered when indicated for the prophylaxis of tetanus in the treatment of injuries sustained by individuals known to have had active service in the Armed Forces of the United States during or subsequent to World War II. The same practice is recommended for other individuals, both children and adults, when there is a reliable history of previous active tetanus immunization." The practical matter as to how to determine accurately whether a given patient has received tetanus toxoid is discussed, and the authors suggest the possibility of establishing a permanent immunization roster, perhaps under the direction of local health authorities, which would afford the vital information needed.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

Congratulations on your handling of the Bloxsom paper in THE JOURNAL OF PEDIATRICS. The discussion approach was very informative. My only regret was that I was so obviously alone in my approval of use of both the Air Lock (in a certain few specific cases) and Alevaire.

Concerning the Air Lock, I feel that the opinion of the other discussors would have carried more weight had they quoted from their own clinical experiences rather than theoretical considerations. Clinical observations would have been of greater value than a mass of proof against theories that were obviously poorly conceived in the first place.

I would like to point out again that I strictly limited the apparent beneficial effects of the Air Lock to the occasional narcotized, limp infant in whom all other resuscitative procedures had failed. An occasional infant of this type will gasp, as though shocked, each time the solenoid "pops off." By simply doubling the rate of flow of both oxygen and air, the cycling rate is doubled, and the infant is made to gasp, two or three times a minute. This carries him along for a while, and in occasional cases normal respiration is finally established. The number of cases is very small, but these few survivors are all infants who were otherwise "dead ducks," as they had already failed to respond to every known resuscitative procedure, up to and including direct rhythmic tracheal insufflation with oxygen.

Insofar as Alevaire is concerned, not a single writer mentioned any personal clinical experiences. Each one mentioning Alevaire pointed to the study of Silverman and Anderson, which was carried out in exactly the manner that I have stated should never be used. I have been stating in talks throughout the country for nearly two years that therapeutic results cannot be achieved in any incubator (such as the Isolette) or tent (such as adult type tents) with blower mechanisms or air-circulating devices. The Silverman study was performed with Isolette incubators, which have a blower mechanism that withdraws the aerosol mist as fast as it can be formed, and condenses it out in the blower compartment. Furthermore the Vapojette nebulizer employed is an inadequately baffled nebulizer, and pours out a tremendous stream of very large drops which drench the infant and the sides of the incubator, and give a superficial appearance of good aerosol therapy. The few floating drops that remain form a thin mist which is drawn off and centrifugally baffled out in the blower compartment.

Another glaring defect of this study is the fact that the infants were started so late on their Alevaire (approximately 9 hours, average). As I have repeatedly stated, it is necessary to *start early*, and use a *dense fog* of *therapeutic-sized* floating particles (which incidentally need not drench the babies' skin or the incubator walls). Aerosol droplets are very small, the tidal volume in these infants is only 15 to 20 c.c. of air, the deposition of Alevaire is thus very slow, and the effect is a slow physical one rather than a rapid chemical or pharmacological one, so ample time for treating this rapidly progressive disease can only be gained by starting almost immediately at birth in all suspected cases, and discontinuing therapy after twelve to twenty-four hours in all infants who did not develop respiratory difficulty. Even so, the secretions are bound to be denser in some cases than others, and other factors such as inherent vigor, maturity, narcosis, etc., play their parts, so not all cases will respond equally well, and time will still run out in some. To statistically evaluate the effects of Alevaire would require a much larger series than reported by Silverman and Anderson, and should include a consideration of all factors, not just the gross mortality rate.

Many similar defects are evident in this study, and they will be taken up in a separate paper.

My type of private practice does not allow me to gather statistical proof of the effects of Alevaire in an entire nursery, but neither

does the study of Silverman and Anderson statistically disprove it. A great many astute pediatricians agree with me as to its clinical value, but properly conducted statistical studies in newborn infants are yet to be reported. I am confident they will be forthcoming and will support the clinically proved effectiveness of Alevaire.

JOSEPH B. MILLER, M.D.

To the Editor:

I was very much interested in the editorial "Is Breast Feeding Worth Salvaging?" which appeared in the October, 1954, issue of THE JOURNAL OF PEDIATRICS.

As one who has been "brought up" to believe in the value of breast feeding, I think it would be highly desirable to set up a Committee on Breast Feeding. In my opinion, such a Committee should be composed of pediatricians, obstetricians, nurses, public health workers, hospital administrators, and representatives from the field of nutrition. It would be well to draw upon organized groups to designate representatives to such a Committee, to explore the "pros" and "cons" of the situation and to devise ways to disseminate factual information and to stimulate interest. Certainly it has been true that many professional personnel and most hospital routines either intentionally or inadvertently have been a discouraging influence on the promotion of breast feeding.

HELEN M. WALLACE, M.D.

To the Editor:

Your recent editorial concerning the apathy of American mothers to breast feeding is a sad reflection on the integrity of the medical profession. This failure to impress young women with the desirability, "availability," and benefits of human milk is the direct indifferent attitude of the obstetrician, pediatrician, and general physician. I agree that it is time to re-evaluate the "blessings" of breast feedings and, as pediatricians, suggest to our obstetrician colleagues that they begin encouraging women to nurse their babies. I will be happy to help in any way possible. I have always felt that medical men are not completely true to their profession when they overlook the advantages of "natural" feeding for infants.

A. M. GROSSMAN, M.D.

P.S. I think the term *"natural feeding"* would be easier to use in the future.

News and Notes

The **American Red Cross** after January 1, 1955, will resume the distribution of *gamma globulin* for use against measles and infectious hepatitis. On that date the Office of Defense Mobilization will end the allocation control which went into effect two years ago for polio prophylaxis. This gamma globulin will not be sold, in accordance with established Red Cross policy, but will be made available through state health departments on a percentage basis.

The **Playtex Park Research Institute,** founded four years ago to support pediatric research, has announced a somewhat changed policy, in which it proposes to sponsor on a one- to three-year basis young investigators whose ideas and programs require financial support. The investigator must have demonstrated an aptitude for research, be associated with a recognized medical institution, and have a proposed program which the Board of the Institute considers challenging and promising. Detailed information as to grants and application forms may be obtained from the Playtex Research Institute, 6415 Empire State Bldg., New York 1, N. Y.

The thirty-second annual meeting of the **American Orthopsychiatric Association** will be held February 28, March 1 and 2, 1955, at the Hotel Sherman, Chicago, Ill.

Book Reviews

Books on Child Care

Last year's output of books on child care, written primarily for lay consumption, showed a little letdown in quantity. Except for the unique illustrated text by Wava McCullough, which was reviewed in the November issue of the JOURNAL, there has been nothing of particular interest and value to the pediatrician. *The Only Child** by Norma E. Cutts and Nicholas Moseley, authors of books on discipline in the home and school, is based largely on studies made on Mount Holyoke, Vassar, and Yale "Onlies." They find, as a whole, that the problems, successes, and failures of the only child are about the same as those found with siblings. It is rather tedious reading due to the constant repetitious use of the terms "Only," "Onlies," and "Onliness." (We counted their use seven times in a paragraph of less than 100 words.) A much shorter analytical study of the "only child" would have been of interest, but the authors have seen fit to go into detail on how to handle the problems such as jealousy and dependence, which are also common and found among siblings, and the advice is simply a repetition of the discussions and statements found in other books. Thus, the text is not centered specifically enough with the problems highlighted by the situation of an only child.

Another unusual book—one of over 1,000 pages and two and one-half inches thick—is *The Encyclopedia of Child Care and Guidance*,† edited by Sidonie M. Gruenberg, who has been a prolific writer in the field. The book purports to be a "comprehensive and practical guide" for all who work with children, such as parents, doctors, teachers, camp directors, and so on. Approximately the first two-thirds consists of brief discussions, often too incomplete to be of value, of a multitude of guidance and medical topics arranged alphabetically. Thus, the first topic is Abilities, the second, Abscesses (for which aspirin is advised to relieve pain), and so on, until the final topic "Wounds. See accident prevention; bleeding; cuts, scrapes, scratches; first aid." We do not believe any reviewer could wade through it all. It is a most curious collection of material—thus, the topic "Crossed Eyes" is followed by "Crossing Streets." The last third of the book if far more interesting. It consists of thirty essays or discussions of particular topics by individuals well qualified to discuss their subjects. "Family Life Is Changing" by Margaret Mead, "The Development of Healthy Personalities in Children" by Benjamin Spock, "How Children Begin to Learn" by Herbert Birch, "How Children Grow" by Nancy Bayley, are a few examples of the topics and authors. While the reader will probably disagree with the viewpoints of the authors at times, this is a matter of personal opinion and not a matter of which is right or wrong. This part of the book is above average. It is difficult to see the rationale of combining this excellent material with the "encyclopedia" part of the book whose value is questionable. Further, it is discouraging and tiring to have to handle a two and one-half inch thick book to get at the last worth-while third. In its entirety it is a curious volume, rather disappointing and unsatisfactory despite the excellent topical discussions.

Klinische Fehldiagnosen, ed. 2. Prof. Dr. M. Bürger, Stuttgart, 1954, Georg Thieme Verlag, 550 pages. Price DM 59.40 ($14.15).

Although this text by the Director of the university medical clinic at Leipzig, with its unusual approach to the problems of differential diagnosis, was first published only two years ago, its reception has led to a second revised and enlarged edition. There is no single word that can be used to translate "Fehldiagnosen." What the author has done is to present in a systematic way a

*The Only Child. A Guide for Parents. Norma E. Cutts and Nicholas Moseley. New York, 1954, G. P. Putnam's Sons, 245 pages. Price $3.50.

†The Encyclopedia of Child Care and Guidance. Edited by Sidonie M. Gruenberg. New York, 1954, Doubleday and Co., 1016 pages. Price $7.50.

series of over 200 cases in which the original clinical diagnosis was wrong, as shown subsequently by the course of the disease, laboratory studies, or pathologic findings. In this way the problems of differential diagnosis are presented in an interesting and instructive way, and the reasons for the error in diagnosis brought out. The discussion is divided in a "general part" of about 100 pages in which the various methods of diagnosis are discussed, and the elements in each which lead to errors in diagnosis. This is an interesting discussion and occasionally bits of wisdom based on experience are presented in a striking way. For example, the heading "Laboratoriumsdiagnose" is followed by a subheading "Omnia sunt dubitanda," and the first sentence is "Gewarnt werden müssen auch vor allem unsere jüngeren Kollegen vor der Überbewertung der sogenannten Laboratoriumsdiagnose." The remainder of the book, the "special part," discusses errors in diagnosis involving the various anatomical systems, the infectious diseases, endocrinologic condition, etc. The cases used to present the problems are clearly presented and discussed. The text is excellently illustrated. While it is not a pediatric text and most concerns problems rarely confronting the pediatrician, there is considerable material of particular interest to the pediatrician, such as errors associated with poliomyelitis, rheumatic fever, and the leukemias. It is an unusual and interesting method of discussing differential diagnosis, and it is a book that is well worth an English translation to make it available to those who do not read German.

Pharmacology in Medicine. Edited by Victor A. Drill, Ph.D., M.D., New York, 1954, McGraw-Hill Book Company, Inc. Price $19.50.

Eighty-one pharmacologists, chiefly of professional rank in medical schools, have contributed to this exhaustive and comprehensive discussion of drugs and their practical use. It is nearly "dictionary size" and a valuable book of reference for the physician or student. The drugs are discussed from the standpoint of their mechanism and action, absorption, excretion, toxicity, and therapeutic use. In all, there are eighteen main headings such as anesthesia, specific chemotherapy, and autonomic nervous system, and a number of chapters or sections under each main heading. It is a very important volume for reference, but too exhaustive for student use as a text.

Die BCG-Schutzimpfung. Rolf Griesbach, Stuttgart, 1954, Georg Thieme Verlag, 330 pages.

This volume on BCG vaccination against tuberculosis written in German has contributions from authors of many nationalities: G. Dahlstrom of Sweden, F. Van Deinse of France, J. Rosenberg of Brazil, H. Spiess, A. Wunderwald, and the Editor of Germany. The book is divided into three main sections: (1) The Basis for BCG Vaccination, (2) Methods and Results of Vaccination, (3) Criticism and Summary.

In the first part, the history of vaccination against tuberculosis is discussed in some detail, and it is shown that the best vaccine at hand from an experimental standpoint in animals is the viable Bacillus, Calmette and Guerin (BCG). Dead organisms, extracts of various sorts, are definitely inferior as vaccines. An interesting experimental study with P_{32} tagged BCG demonstrated that when the vaccine was introduced by the multiple puncture technique, two to four times as many organisms were recovered from the internal organs as compared with the intradermal method.

The relatively few complications following vaccination in human beings is discussed. The local accelerated reactions can be reduced by pretesting with at least 1 mg. of old tuberculin.

In the second part, the oral method of vaccination as practiced in Brazil is discussed. In newborn infants, as much as 600 mg. is given during the first five months of life (concurrent method of Arlindo de Assis). The highest percentage of tuberculin reactors following this method is after twelve weeks when 33.5 per cent react to up to 10 mg. of O.T. Following 100 mg. dose of vaccine, 87.7 per cent will react to tuberculin. The difference in results is explained by a desensitization having taken place with the larger dose. Oral vaccination in tuberculin-positive reactors has been practiced and a desensitization is noted. A

certain degree of protection against tuberculosis is recorded, but the number of acceptable experiments is limited.

The lepromin reaction becomes positive after oral BCG vaccination. BCG vaccination is recommended against leprosy.

The more common methods of vaccination by BCG are given in some detail. This includes the multiple puncture method of Rosenthal, the scarification method of Negre and Bretey, and the intradermal method as described by Wallgren.

A brief survey of the world literature is cited with special chapters on the Scandinavian and German experiences. Approximately 100 million vaccinations have been done throughout the world; 28,820,862 vaccinations by the International Tuberculosis Campaign groups alone; 2,796,771 vaccinations in Germany. The results as far as reducing the incidence of tuberculosis in the vaccinated as compared with the controls have been uniformly favorable. Statistics are quoted from all parts of the world.

In the third part, some of the arguments against BCG are dealt with. The reports from the literature of untoward effects or increased virulence are discussed. In an analysis of the reports of deaths from tuberculosis in BCG-vaccinated individuals, no proved cases are apparent where the fatal issue was the direct result of the vaccination. In answer to J. Arthur Myers (Minneapolis), who claims that tuberculosis can be controlled by simply isolating the source case and practicing the known hygienic measures for controlling tuberculosis, is cited the war-torn areas of Europe and Japan and the fact that in Japan alone there are 1,500,000 open cases of tuberculosis and only 100,000 beds! (In some of the densely populated areas of the U. S. A. the situation will not readily approach the Utopia, so far as tuberculosis is concerned, that exists in rural Minnesota.)

In summarizing, it appears evident that immunity against tuberculosis is bound up with viable tubercle bacilli. BCG is the vaccine of choice. Of all active immunizations, BCG gives the least complications and thus is the least harmful. BCG is beyond the experimental stage and is an effective method of increasing the resistance against tuberculosis.

This volume, written by authors who have had personal experience with BCG from an experimental and a clinical standpoint, is recommended for those working in the laboratory as well as in clinical practice. It has an extensive bibliography and outlines details of vaccination programs in all age groups, including clinical forms, etc.

Atlas of Congenital Cardiac Disease. Maude E. Abbott, New York, 1936, American Heart Association. Price $5.00.

This classic monograph on congenital cardiac disease has been reprinted (1954) in facsimile form by the American Heart Association. Fifteen hundred numbered copies have been printed. The Atlas is so well known and so frequently referred to in medical literature that it needs no description or discussion. With the increase in interest in congenital cardiac disease following the developments in diagnosis and therapeutics which have taken place in the last fifteen years, the Atlas, which has been out of print for a number of years, has become difficult to obtain. The Heart Association by this facsimile reproduction has not only paid a well-deserved tribute to a great student and investigator who died in 1940, but has helped meet a distinct need. The pathologists and pediatricians owe the Association their sincere thanks.

Growth and Development of Children, ed. 2. E. H. Watson, M.D., and George H. Lowrey, M.D., Chicago, 1954, The Year Book Publishers, Inc., 296 pages. Price $7.00.

The first edition published only three years ago was very favorably received and required a reprinting. In the new edition, numerous changes have been made, particularly in relation to physical growth. A new chapter discusses the growth and development of the jaws and teeth. The text has been particularly useful for those preparing for the examination of the American Board of Pediatrics.

Editor's Column

SCHIZOPHRENIA AND ADRENALINE

THE production by adrenochrome of psychologic states resembling those found in schizophrenia has recently been reported by Hoffer, Osmond, and Smythies of Saskatchewan.[1] This observation has special significance in that adrenochrome is probably a normal product in human metabolism.

When adrenochrome was administered to a number of human volunteers variable mental syndromes followed. Dr. Hoffer became overactive, showed poor judgment and lack of insight. Mrs. Hoffer became severely depressed and remained in this state for four days. She, too, showed lack of insight and was unable to relate her depression to the injection of adrenochrome. The prolongation of symptoms may have been due to an attack of infectious hepatitis some years earlier.

Another subject, Dr. Osmond, responded to an injection of adrenochrome with visual hallucinations: The ceiling changed color, the lighting appeared brighter, brightly colored patterns of dots appeared when the eyes were closed, which resolved themselves into fishlike shapes. The Rorschach cards, which were familiar to the subject, were changed in an extraordinary manner. They were different in texture and in bas relief appearance and the shapes were strange and amusing. This subject felt cut off from people but he was not unhappy. He speculated as to whether he was really a person or merely a plant or a stone. Interest in human beings dwindled. Changes noted by his co-workers were preoccupation with inanimate objects, negativism, loosening of the associative process, anxiety, and distractibility.

Adrenochrome is one of the numerous substances with a chemical structure similar to adrenaline and mescaline. However, it does not produce the gross physiologic effects of adrenaline nor the clouding of consciousness and confusion of mescaline.

Adrenochrome was discovered by Green and Richter[2] in 1937 who found that it acted as a hydrogen carrier in concentrations which are physiologic. It was present in skeletal muscle in minute amounts. There is some doubt as to its presence in the human body.

Adrenaline is disposed of[3] in the body by (1) excretion in the urine, (2) storage in the cells, (3) deamination to form oxidizable aldehydes, (4) esterification of the phenol hydroxyls, and (5) quinone formation to adrenochrome. Interference with any of the first four mechanisms may lead to an increased production of adrenochrome.

Woodford[4] has shown that, when adrenochrome enters the brain cells, it inhibits markedly the intermediary metabolism of carbohydrates. To demonstrate that adrenochrome can cross the blood-brain barrier, electroencephalographic tracings were made. It was possible to demonstrate changes in epileptics with normal electroencephalograms within a half hour after administration and the experimenters are now using adrenochrome routinely in establishing the diagnosis of epilepsy since it so clearly brings out the epileptic activity.

Adrenochrome inhibits hexokinase under anaerobic conditions.[5] It also inhibits the aerobic oxidation of glucose and pyruvate.

The observations of Hoffer, Osmond, and Smythies suggest that a schizophrenia-like syndrome can be produced in human beings by the administration of a substance, adrenochrome, which probably occurs in the human body. Adrenochrome, unlike adrenaline, can cross the blood-brain barrier where it interferes with aerobic and anaerobic respiration.

Rinkel, Hyde, and Solomon[6] have been using the recently discovered diethylamide tartrate of d-lysergic acid (LSD) to induce psychotic conditions. It is their view that LSD acts by interference somewhere within the adrenaline cycle.

These workers were unable to produce psychotic symptoms in themselves or in volunteers with commercial adrenochrome, nor have mental alterations been observed in surgical patients in whom it has been used because of its strongly hemostatic effect. They suggest that the results obtained by Hoffer, Osmond, and Smythies were not due to adrenochrome but, possibly, to adrenoxin, a further oxidation product of adrenaline which may have been present in the impure preparation used. Adrenoxin is an unstable metabolite of adrenaline, obtained by prolonging the oxidation of adrenaline beyond the adrenochrome level.

The evidence of various workers points to a relationship between schizophrenia and the metabolism of adrenaline.

H. B.

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FLUORIDATION FOR THE PREVENTION OF DENTAL CARIES

FEW proposed public health measures have been the subject of so much controversy and acrimony as the fluoridation of community water supplies to prevent dental caries. Despite the endorsement of the program by dental, medical, and health scientific organizations, vociferous opposition exists.

Certain facts are clear and definite. In communities where there is an appreciable natural fluoride content in the water the extent of dental caries is only one-third of that found in communities where fluorides are absent. Many examples could be quoted. An excellent one is two cities in northern Illinois. In Galesburg, where the natural fluoride content of the water is 1.8 parts per million (ppm), a survey of children 12 to 14 years of age showed 201 carious defects per 100 children, while in Waukegan, where the natural content is 0, the extent of caries reached 810 per 100 children. These children had been living and brought up in communities where the public water supply had

natural differences in the fluoride content.

Other studies with similar findings in a number of communities led to the proposal that fluoride be added to the water supply in communities where the content is less than 1 ppm. The suggestion that fluorides be incorporated in the diet because of their importance in the maintenance of teeth is not new, as back in 1892 it was suggested by Crichton-Browne in England. However, it has not been until recent years that fluoridation as a public health measure has been suggested, and it was not until 1945 that studies were started to determine the effect of fluoridation. Controlled studies in Grand Rapids, Michigan; Brantford, Ontario; Newburg, New York; Evanston, Illinois; Sheboygan, Wisconsin, and other cities, continuing for from seven to nine years, have shown that the incidence of dental caries can be decreased roughly two-thirds in the 6-year-old age group, and one-half in the 8- to 9-year age group. The results of these studies have led to a widespread movement, sponsored by dental and medical societies and departments of public health, to have fluorides added to the public water supply in communities where the natural content is less than 1 ppm. As a result, fluoridation is now being done in over one thousand communities with a total population of around 20,000,000. Both Chicago and St. Louis will start fluoridation in 1955, and there is every reason to believe that the population coverage will be rapidly extended in the next few years. There can be no question but that caries resistance is in some way related to the fluoride content of the water supply. Water fluoridated by nature, or by addition to make the content 1 ppm, produces the same 60 to 65 per cent reduction in caries.

Despite the fact that fluoridation has been more carefully studied than any previous proposed health program, there has been strong opposition which still exists. While most of this has been led by cultists, and those "congenitally resistant" on the basis of individual rights being more important than public good, there are still a few physicians and dentists who are somewhat skeptical of its value. Most of the objections have been on an emotional rather than a rational basis and reveal an ignorance of the background of the program. On the other hand, there have been some important questions raised. The most important is that fluorine might act as a poison, and the question is, could fluoridation cause acute or chronic poisoning? There are many substances necessary for health that are harmless in small quantities, but which become poisonous if used in large amounts. Iron, for example, which has been used for generations to prevent anemia, is of the greatest value when used in proper dosage, and it is found in foods and water, but it has caused the death of children when taken accidentally in excessive amounts. The point is not whether sodium fluoride is a poison, but whether or not sodium fluoride in a concentration of 1 ppm is poisonous. Of the millions of people who for generations have been drinking water containing 1 ppm, not one has been shown to have suffered any harmful effects. To be toxic the fluorine content of the water would have to be many hundred times this level. The idea has even been put forward that excessive fluoridation might be an easy method of sabotage. Shaw esti-

mates that it would require 2.1 tons of fluorides to bring the content of the 210 millions of gallons of water used in Greater Boston on an average summer day up to 1 ppm. To raise this to a level that might cause acute toxicity (1,000 ppm) would require the addition of 2,100 tons, or fifty boxcar loads. The question of acute poisoning from fluoridation can be dismissed.

More important is the question of chronic poisoning from the long-continued ingestion of fluorine. Could it lead to an increase of degenerative disease of a vascular nature, or even cancer, has been asked. In some communities where the level of fluoride in the water is naturally high (8 to 10 ppm) there is a decided and recognized incidence of "mottled teeth," which is esthetically disfiguring. An incidence of disfiguring mottled enamel, however, has never been seen in a community where the natural level is 1 ppm. The condition has first been noted to appear when the natural level is above 1.5 ppm. Carefully controlled studies of communities with high and low fluoride contents, where the inhabitants have been drinking the water for generations, fail to show in the communities with a high level any increase in the mortality, or decrease in longevity rates, or an increase in the incidence of cardiovascular or kidney diseases, of cancer, or of any other disease. One report, much publicized by opponents, purporting to show an increased incidence of cardiovascular diseases in Grand Rapids after fluoridation, was found to be based on distorted statistics, and a careful revaluation of the statistics failed to show the increased incidence. So much for the question of poisoning.

Another question that deserves consideration is why, if the value of fluorides is chiefly on the development of the teeth in young children, is it necessary or desirable to fluoridate the entire water supply which is chiefly used for other purposes, such as washing, bathing, lawn sprinkling, etc. Fluoridation of the communal water supply is the recommended method of procedure because it is by far the cheapest way of bringing to all children the benefits of fluoride. Further, it is the only method by which the daily intake can be simply and effectively controlled. The cost of one filling of a carious tooth will pay for thirty years of fluoridation for that child. The four-time topical application of fluoride to the teeth is less effective and much more expensive, and, if applied to all children, could not be carried out by our present number of dentists and dental hygienists.

To anyone unbiased by emotion who studies the evidence, the conclusion is inevitable that fluoridation is a safe and sound public health program for reducing dental caries. In every community where the natural fluoride content is less than 1 ppm, it should have the support of the pediatricians, who have always pioneered and supported preventive medicine. Dental caries is the most common physical defect found in every health survey of children that has been made. It must not be forgotten, however, that it is a preventive measure with quantitative limitations, and the moot question as to what causes dental caries still remains.

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